disease have side effects that represent a threat to the patient, that is something that would not be good for their health. Tolerability is how well the patient does taking the drug as far as day-to-day symptoms, which may or may not be dangerous, but influence whether they're going to continue to take the drug.

Q. Have you helped prepare a slide that shows when the various treatments for relapsing remitting MS were approved by the FDA?

A. Yes, I have.

Q. Let's pull that up slide 9. Dr. Lisak, could you walk us through what's here?

A. The dates are your time line, so 1990s through essentially last year. And on the top are the first line therapies and below the horizontal time line are the second line therapies as well as the new oral medication Gilenya. As I said earlier, I don't think we know how it's going to be viewed, it's too soon.

Q. I'm sorry, sir, if you already mentioned this, but which of these are the first line therapy?

A. The ones above; Betaseron, Avonex, Rebif and Extavia are the interferons and Copaxone is the non-interferon, those are the ones above the line.

Q. And the ones below are second line treatments?

A. The ones I mentioned earlier, below the line Novantrone and Tysabri. I mentioned Gilenya is listed below the line, but it's not been a year so we don't know how it will be viewed

eventually.

Q. Before the introduction of these disease modifying agents, how was MS treated?

A. We treated symptoms and we treated relapses short term with corticosteroids. Prednisone is a good example of what we used. So we treated relapses, which shortened the duration of relapses, but it didn't prevent the next one and it didn't have any effect on disability from repeated attacks.

Q. Are some of these first line agents referred to as interferon therapies?

A. Yes, the Betaseron Avonex and Rebif and Extavia, they're interferons.

Q. How do these interferon treatments work?

A. They work by increasing the ability of inflammatory immune cells that are depicted in one of the earlier illustrations from getting into the brain and spinal cord. That's the major way we think they work.

Q. Are there any major differences in how these various interferon treatments work?

A. No.

Q. Could you please describe the efficacy of the interferon treatments?

A. Yes. They reduce the number of relapses, they make them less severe, they lengthen the period between them and there are studies that have shown reduction in disability, delaying

of disability as well as reduction in number and size of new lesions on the MRI scan.

Q. Are these interferon treatments effective for all patients?

A. No, they are not.

Q. About how many or what percentage of the patients do they work for?

A. I would say sustained probably about 60 percent or so.

Q. Is there any reason why these treatments don't work for all patients?

A. One is that MS is a complex disease and you may need a drug that has a different mechanism or way of attacking the MS process. And the other is that interferons reduce something called neutralizing antibodies.

Q. What are neutralizing antibodies?

A. When you inject the patient with interferon or any protein, they make antibodies and some of those antibodies block the biologic effect of interferon. So if you're taking interferon and you have what we call high titers of neutralizing antibodies, the drug stops working for you and there are many studies that demonstrate that neutralizing antibodies block the effect of interferons to either clinically or through MRI scan help the patient.

Q. How common is it for these neutralizing antibodies to develop?

A. There are studies that range from about 5 to let's say

30 percent usually appearing within 6 to 18 or 24 months of when the patient initiates one of the interferon therapies.

Q. Are there any major differences between any of these interferon treatments and their side effects?

A. Perhaps the frequency of flu-like is a little less with Avonex since Avonex as Mr. Congleton mentioned is injected into the muscle. You don't get the so-called skin reactions because the reaction is going to be in the muscle where you can't see it, but certainly flu like and some of the other side effects are the same.

Q. What are the typical side effects of these interferon treatments?

A. Well, again, for those who are injected subcutaneously, with Betaseron, Rebif and Extavia you have redness, pain, itching at the site of injection. Sometimes rarely some breakdown of the skin. There's what we call flu-like reaction. So patients when they take the medication feel as if they have the flu and that's because when you have the flu your body makes interferon, and so not surprising that that would happen, so you get fever, chills, achy muscles, achy joints, headache, you feel like you have the flu.

They also have side effects that affect liver function and can suppress bone marrow blood counts, representing bone marrow supression. They're also able, unfortunately, to increase certain symptoms that MS patients may already have

such as stiffness from spacicity. You can increase fatigue and it can increase and sometimes be associated with the new appearance of depression, so those are the side effects of interferon, all of them.

Q. Do any of these side effects require additional treatment?

A. Yes, certainly the flu-like for many patients requires them taking the same medicines we would all take for the flu, so aspirin, acetaminophen, which is Tylenol, Motrin, Aleve, medications like that. Then, of course, if you're taking those medicines they have their own side effects and their own safety issues, so you're taking in many cases another medicine so that you can take the interferon.

Q. As a physician, could you monitor patients that are taking interferon therapy?

A. Yes, the prescribing guidelines are for frequent, several times a year assessing liver function tests and blood count to assess whether there's any supression of the bone marrow function.

Q. As of 1994 were the interferon treatments considered effective for all MS patients?

A. No.

Q. About what percent of the patients, MS patients at that time were not able to be treated with interferon?

A. Well, we know that about 20 to 30 percent stopped taking it roughly for tolerability issues, and then we know that in the

original Betaseron as many as 20 or 25 percent in that study developed neutralizing antibodies, so with the Betaseron alone that would be 40 percent. So that's where my guesstimate, estimate of 60 percent benefit will return from the interferon so 40 percent roughly have not and those numbers have seen help.

Q. When did the first non-interferon disease-modifying agent become available?

A. That would be Copaxone. It was approved in 1996, available in 1997.

Q. To this day, are there any other first line therapies other than Copaxone that are not interferons?

A. None that are considered first line at this time.

Q. Let's talk about the efficacy of Copaxone. Can you generally describe its clinical efficacy?

A. Yes, it reduces relapses, it lengthens the times between relapses. It makes the relapses less severe than placebo treated patients, untreated patients. In other studies it has been shown to have a beneficial effect with MRI scan and reduces and delays disability.

Q. When was the first large scale clinical study of Copaxone?

A. That was presented as a paper in 1987. That's when the paper was published.

Q. When was the first large scale study of Copaxone, sir?

A. The large scale? I'm sorry.

Q. Yes.
A. I misunderstood. The first large scale would have been the Johnson study which is published in '95, '95 or '96. I'm sorry, I thought you said the first study.
Q. That's okay.
A. My mistake.
Q. Were you involved in that Johnson study?
A. Yes, I was.
Q. What was your involvement?
A. I was the principal investigator at Wayne State University.
Q. And what were your responsibilities in that role?
A. Involved in examining and doing the neurologic history, side effect history of patients as well as supervising the staff and the other neurologists involved in the study.
Q. What year did the Johnson trial begin?
A. First patients were enrolled in October of 1991.
Q. How long did it last?
A. It was a two-year trial. Not all patients get in on day one, officially. So end of '93, early '94 I would say would be the last patient analyzed.
Q. How many patients participated in the study?
A. Nationally, 251.
Q. Of the 251 patients, how many were at Wayne State?
A. 24.
Q. What were the results of that trial?

A. Results were that it was demonstrated that the medication was effective, met its primary outcome of reduction in relapse rate. Also secondary outcomes of less severe attacks, time between attacks and some evidence of delay in disability.

Q. When were the results of that trial made publicly available?

A. The presentation at the American Neurologic Association I believe was in late '94 and the paper was published I believe in 1995.

Q. Are you a co-author on that study, sir?

A. Yes, I am.

Q. If you could turn to tab PTX597 in your binder. Do you recognize that document?

A. Yes, I do.

Q. What is it?

A. It's a copy of the paper to which I referred, the so-called Johnson study in the Journal of Neurology.

MR. BENNETT: Your Honor, plaintiffs move the admission of PTX597.

THE COURT: Any objection?

MS. BLOODWORTH: No, your Honor.

MR. DOYLE: None.

THE COURT: All right, admitted.

(Plaintiff's Exhibit PTX 597 received in evidence)

Q. Dr. Lisak, as part of the publication of the results from

the Johnson trial has any study been done for the efficacy of copolymer-1's against relapsing remitting multiple sclerosis?

A. Yes.

Q. Is that the Bornstein trial that you referred to?

A. That's the trial I referred to, the Bornstein trial, which is the 1987 publication.

Q. Was the Bornstein trial a pilot trial, sir?

A. Yes.

Q. What is a pilot trial?

A. Pilot trial is a therapeutic trial which is usually smaller and is designed to see if there's a trend or something encouraging that the drug in question might be effective and would be reasonably safe.

MR. BENNETT: Your Honor, just for the record, the '87 Bornstein trial was admitted as PTX31 in the July trial.

THE COURT: All right.

Q. And again, sir, are pilot trials used to draw conclusions as to the efficacy or safety of a specialty treatment?

A. They're not conclusive, no.

Q. And, again, why is that?

A. Numbers are small and in a heterogeneous unpredictable disease like MS and other autoimmune diseases you need larger numbers to be certain if you have an efficacious drug.

Q. Generally, what were the results of Dr. Bornstein's '87 study?

A. There was a reduction in relapse rate, increased period between relapses, and less disability in the treated group compared to the placebo group. They were 25 in each group, placebo and treated, 25 each.

Q. Were there any side effects reported in that study?

A. Yes, there were.

Q. In general what were those side effects?

A. Injection site reactions in the skin, redness, itching, pain, occasional hives and then something that has become called the post injection immediate hyper sensitivity reaction.

Q. Were there any differences in the copolymer-1 used in the Bornstein trial and the Johnson trial?

A. Yes, there were.

Q. Just briefly what was that difference?

A. The molecular weight, the average molecular weight or range of molecular weights, I should say.

Q. And what is your understanding as to what that difference was?

A. In the Johnson trial, we were examining material that was 4.7 to 13 kilodaltons. In the Bornstein I believe it was 14 to 23 kilodaltons.

Q. Before the results of the Johnson trial were published, was it known that copolymer-1 was an effective drug?

A. No.

Q. Why is that?

A. Because the Bornstein trial was, while controlled, was quite small total number and certainly the number treated was quite small.

Q. And what was the -- why did you know after the Johnson trial had been completed that copolymer-1 was effective?

A. It was a large study. It was randomized, placebo-controlled and it was actually double blinded, so the patients didn't know what they were getting. Both neurologists and the nurse who dealt with them did not know what they were getting. Bornstein trial smaller and the person who was asking about side effects was not a physician or a nurse necessarily, and knew what the patient was on, whether they were on placebo or active so it's not as large and it's not as rigorous.

Q. Before the results of the Johnson study were published, was it known that copolymer-1 could be used safely in humans?

A. No, it was not.

Q. Again, why is that?

A. Well, if you have a study of 50 patients only 25 of whom are getting the active drug compared to the placebo, you would have no real way of knowing if some side effect might show up that only shows up if 100 people are on it or 50 people or 70, so just too small to say.

Q. Following the completion of the Johnson study, have further clinical studies been performed with Copaxone?

A. Yes, they have.

Q. Have you helped prepare some slides that describe the findings of those studies, sir?

A. Yes, I have.

MR. BENNETT: Let's pull those up. Slide number 10. If you need to, Dr. Lisak, we have those articles in your binder as well, but refer to the slide. Can you describe for us what we're seeing here which is a reference to PTX633?

A. Yes, this is a paper published in the Journal of Neurology, first author is Massimo Filippi from Milan, and this is a study done in Europe and in Canada in relapsing remitting multiple sclerosis and in this article they are looking at the ability of glatiramer acetate compared to placebo to reduce the portion of patients with MS that get what we call lesions that become black holes. Black hole, without getting too technical, is an area which is decreased density and represents permanent loss of myelin polyandrous axons so it's an area of focal atrophy.

This article says in these patients there is less of that occurring in patients treated with glatiramer than in the placebo group.

Q. What is the impact of forming black holes on a patient?

A. Black holes being a permanent loss of myelin and the axons and neuro response means that that is permanent disability. It's a mark of permanent disability.

Q. Have any interferon treatments been proven to show an effect on black holes?

A. Not that I know of, no.

MR. BENNETT: Plaintiffs offer PTX633 into evidence.

THE COURT: Any objection?

MS. BLOODWORTH: No, your Honor.

MR. DOYLE: No, your Honor.

THE COURT: All right, admitted.

(Plaintiff's Exhibit PTX 633 received in evidence)

Q. Dr. Lisak, let's go to slide number 11. Again, this is PTX632. Explain to us what we're seeing here.

A. This is an article in the Annals of Neurology. It is another aspect of the same group of patients, the European Canadian study and they were looking at different MRI end points. In this case they were looking at the number and the size of those lesions that I showed you earlier and whether there were less new ones seen in the treated patients versus the placebo-treated patients and the conclusion was that there were less new lesions and they were smaller and there were less lesions seen.

So again, a positive outcome, slightly different MRI metric, looking at the same patient group.

MR. BENNETT: Plaintiffs move for the admission of PTX632.

MR. DOYLE: No objection.

MS. BLOODWORTH: No objection, your Honor.

THE COURT: All right admitted.

(Plaintiff's Exhibit PTX 632 received in evidence)

Q. Dr. Lisak, let's move on to the next slide, number 12. What is depicted here?

A. This is a long-term perspective extension study of the original Johnson study and the original was two years. We then published a controlled series because some of the patients were still finishing up a three-year and these are the long term studies and this one is looking at patients at a ten year time point and we published earlier time points as well, and the conclusion in this is that patients continue to do well and that the drug continues to be well tolerated and no serious side effects that are not seen in the first two years and three years, none have come forward, none have appeared.

Q. Are you one of the authors on this article?

A. Yes, I am.

MR. BENNETT: Plaintiffs move for the admission of PTX668.

THE COURT: Any objection?

MS. BLOODWORTH: No, your Honor.

MR. DOYLE: No, your Honor.

THE COURT: Admitted.

(Plaintiff's Exhibit PTX 668 received in evidence)

Q. Let's move on to slide number 13. Again, Dr. Lisak, what is described here?

A. This is a study of something called clinically isolated

syndrome. Mr. Congleton alluded to it. That's the first attack of the typical symptom of MS in a clinical setting, a young person between 20 and 40 that is likely to be the first attack of MS and the MRI scan makes it pretty clear that that's what they really have, the first attack of MS, and if you treat patients in this study with glatiramer acetate versus placebo and follow them, there's a reduction in the number of patients who go on to meet the criteria for MS, meaning a second attack during the observation period. So that's this paper that you see in front of you here.

MR. BENNETT: Plaintiffs offer PTX680 into evidence.

MS. BLOODWORTH: No objection.

MR. DOYLE: No objection.

THE COURT: All right, admitted.

(Plaintiff's Exhibit PTX 680 received in evidence)

Q. We just talked a little bit about the efficacy of Copaxone. Could you now describe for us, sir, the typical side effects of the treatment?

A. Yes. There are injection site reactions, so that's redness, pain, redness and erythema, pain, itching, occasional skin necrosis. Some patients develop what we call lipo atrophy, a little dimpling of the skin at the sites of frequent injections and those are the injection site reactions. Then there's the hyper sensitivity post injection reaction that I described earlier when we talked about Dr. Bornstein's study.

Q. How common are those systemic side effects that you referenced?
A. It varies in the studies. It affects somewhere between five to perhaps 15 percent of patients will have one or more during a two-year period of observation. So average 10 percent, but it doesn't mean 10 percent of every injection, obviously.
Q. And how common are the injection site reactions?
A. Those vary again, depending, some of those I mentioned go together, so it can be painful and red at the same time. So you can't just add them up. 60 to about 80 percent would be from, if you look at all the Copaxone studies, that would be about the range.
Q. Those reactions occur, is that 60 to 80 percent of all injections, sir?
A. No it's 60 to 80 percent of patients will have during the period of their being observed will have one or more of those, but it may only be one. So it's not with every injection.
Q. As a physician, do you consider those injection site reactions to be a safety issue?
A. They're not a safety issue.
Q. How frequently do patients discontinue Copaxone therapy because of these side effects?
A. In my clinical observation it's uncommon and in the studies it's relatively uncommon.

Q. In your opinion, how do the side effects of Copaxone compare with the side effects of the interferon treatments we talked about earlier?

A. Well, the Copaxone does not induce the flu-like syndrome. It does not worsen fatigue, stiffness, or seem to cause or increase depression, and it is favorable in my opinion because there's no worry about liver function or bone marrow supression. And I don't need to treat with another drug to avoid a flu-like, since it doesn't cause it.

Q. Does Copaxone have any tendency to exacerbate pre-existing conditions?

A. Does not increase pre-existing symptoms, nor does it increase problems with pre-existing other diseases. There's some issue with psoriasis and the interferon thyroid disease, for example.

Q. How does the efficacy of Copaxone compare to the interferon treatments?

A. In typical trials they were not head to head. They seem to have the same reduction in relapse rate, about 29 to 33 percent. But in head to head studies, which were done and announced in the 2005 to 2007 years and were published in 2006-2007, they turned out to be equally effective at reducing relapse rate, disability markers and MRI.

Q. Does Copaxone cause the production of those neutralizing antibodies we talked about earlier?

A. No, there are no neutralizing antibodies that were shown with Copaxone that inactivate the drug.

Q. Do we know precisely how Copaxone works?

A. We know a lot of the different mechanisms that Copaxone seems to do to the immune systems. We don't know which ones are the most important at any one time. So we know somewhat how it works, but not the final steps and why it works on an individual patient.

Q. Do we know whether Copaxone works differently than the interferons?

A. Yes we do.

Q. How do we know that?

A. You could do laboratory studies which have been done on the blood and other ways of looking at patients with treatment with Copaxone or the interferons and show there are different ways that the laboratory tests change and there are different mechanisms that would be important in MS, plus we know that the interferons work through a certain signaling mechanism in the body and that does not use that same signaling category.

Q. Is that difference in how Copaxone works from interferons important to you as a clinician?

A. Yes, it is.

Q. Why is that?

A. One, it gives me a drug that has a different way of acting in a patient who may not respond to the interferon, so the

interferon mechanism of action may not be the best for that particular patient at that time, and also I don't have to worry about neutralizing antibodies so that's a difference. Also the mechanism of action, since it only interacts with certain cells of the immune system, Copaxone, it doesn't cause bone marrow suppression or liver function tests because it doesn't interact with those elements in the body.

Q. Dr. Lisak, what first line treatments do you currently describe?

A. Copaxone and the interferons.

Q. Is there any one treatment that you prescribe for frequently?

A. I prescribe Copaxone more frequently.

Q. Why is that?

A. Well tolerated, no other medications need to be given with it. There's no safety issues, I don't have to monitor blood counts and liver function tests. I don't have to worry about medications that I'm giving them to get rid of the flu-like reaction and in my clinical estimate as well as the studies, it works.

Q. I apologize if you already mentioned this. About what percentage of your patients do you prescribe Copaxone to?

A. Currently it would be around 70 percent are on that as their initial therapy.

Q. Has your prescribing behavior changed over time?

A. Yes, it has.

Q. Why is that?

A. With additional studies showing efficacy and with my own clinical practice, I've been very pleased with the patients' ability to tolerate it in what seems to be a large percentage of them, they continue to do well with very few relapses and they seem to be injecting the drug on a regular basis because they seem to be tolerating the tolerability effects and there seems to be no serious side effects.

MR. BENNETT: Your Honor, we're at a natural breaking point here. I don't know what you have planned for lunch.

THE COURT: Do you have some idea of how much longer your direct is?

MR. BENNETT: I think it would be somewhere between 30 to 45 minutes.

THE COURT: All right. Why don't we break now and I'll see everybody back at 1:30.

(Luncheon recess)

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AFTERNOON SESSION

(1:35 p.m.)

THE COURT: Mr. Bennett, you may proceed.

BY MS. BLOODWORTH:

Q. Dr. Lisak, you talked about the first line therapies available for RRMS. I'd like to talk about the second line

treatments available. What second line treatments are currently available to treat the disease?

A. FDA approved are Novantrone and Tysabri.

Q. Could you describe generally the efficacy of Novantrone?

A. Novantrone reduces relapses, has a beneficial effect on MRI scan and shows the ability to delay depression compared to the placebo treated patients.

Q. Why is Novantrone considered a second line therapy?

A. It's actually a chemotherapy drug originally developed for cancer, and has significant very dangerous side effects.

Q. Could you describe what those side effects are, sir?

A. Well, it has the usual chemotherapy, which is nausea, vomiting, hair loss, things like that, but it has two significant side effects, one is it's cardiotoxic, that is, it damages the heart and the other is that it's associated with an increased incidence of leukemia.

Q. How frequently does leukemia develop in patients taking Novantrone?

A. In the MS population it seems to be about 1 to 2 percent of the patients.

Q. Are there any other side effects that are typical of that treatment?

A. As I mentioned, it is a cardiotoxic agent, so it can cause heart damage and can lead to heart failure.

Q. When you're prescribing Novantrone, do you need to monitor

your patients?
A. Yes. Besides the blood count liver function tests and things like that, you have to get a cardiac test before each infusion, something called an echocardiogram for example, and then actually even after the patient is off the drug, the FDA now suggests or I think may even require that you get a yearly echocardiogram on the patient for the rest of their life.
Q. Does the FDA require any specific warnings about Novantrone?
A. Yes, Novantrone has what's called a black box warning for the cardiac toxicity.
Q. What is a black box warning?
A. It's a warning right after the beginning of the prescribing information for side effects that the FDA wants to make sure that is brought to the attention of the prescribing physicians because they feel it's significant and very dangerous.
Q. What other second line therapies are currently available to treat RRMS?
A. Tysabri is the other.
Q. What is Tysabri?
A. Tysabri is something called monoclonal antibody and it's infused every 28 days and that's Tysabri.
Q. Could you generally describe for us the efficacy of Tysabri?
A. Tysabri, which blocks certain cells from getting into the

nervous system is associated with reduction in relapses, less severe relapses. It's associated with improvement of some of the MRI metrics, measurements that I demonstrated that patients get. So those are the benefits of Tysabri.

Q. What are the typical side effects of Tysabri?

A. Like any immuno globulin infusion, there's sometimes headaches, back pain, hives, chills. Those are transient, usually not a major issue. Tysabri is associated with a viral infection of the brain called PML, which stands for progressive multi focal leukoencephalopathy, so PML, easier to say.

Q. Could you just expand on what exactly PML is, sir?

A. PML is a viral infection of the brain with a virus that's called a JC virus, and about 50 percent of the population carry that virus around in them, but in patients who have immuno supression, a certain percentage of those, actually AIDS is the best example, get this virus that goes into the brain and becomes infectious and causes neurologic dysfunction.

Q. Are there any other effects from PML that a patient can experience?

A. Well, patients have died from PML, including patients being treated with Tysabri for multiple sclerosis.

Q. Does Tysabri have a black box warning as well, sir?

A. It has a black box warning for PML.

Q. Other than Tysabri and Novantrone, are there any other second line treatments that are currently available?

A. As I mentioned earlier this morning, Gilenya, it's too soon to be said. I don't think you could characterize it as first or second line yet. It's just new.

Q. So focusing on the treatments that are clearly second line treatments, how do the side effects for those treatments, specifically Novantrone and Tysabri compare to Copaxone?

A. Well, there are much more serious -- Copaxone has no effect on blood count or liver function tests, it's not associated with PML, it's not cardiotoxic, and, so those two most significant, and it doesn't produce leukemia, so the serious ones are Novantrone, cardiotoxic and leukemia and the most serious one of Tysabri, which is PML are not associated with Copaxone at all.

Q. Now you mentioned Gilenya. Could you remind us when that was approved?

A. Gilenya was approved last year and I think it became available November of last year, I think it was August or something like that of last year.

Q. What do we know about the efficacy of Gilenya?

A. We know it reduces relapses. We know that it again has good effect on the MRI, less lesions, less fine lesions, less new lesions, and it seems to be a beneficial effect on disability, slows disability and reverses the treating group versus the non-treating group.

Q. What side effects are associated with the use of Gilenya?

A. The first dose of Gilenya is associated with a slowing of the pulse, dramatic slowing which requires monitoring and if you stop the drug and then restart it again, do it again, it is associated with an increase in infections, particularly broncho pneumonia and bronchitis. It's associated with swelling of the retina at the back of the eye, there is a slight increase in hypertension in patients and in patients who don't have immunity to certain viruses, in particular the chicken pox shingle virus that's been associated with a chicken pox varicella encephalitis.

Q. You previously mentioned that MS was first recognized as a distinct disease in the 1860's, right?

A. That's correct.

Q. Between the 1860's and 1993, were there any agents available to treat relapsing remitting multiple sclerosis?

A. Only treating symptoms and treating relapses, but none to treat or prevent, treatment that would prevent relapses or make relapses milder and nothing that would have any effect on eventual disability or progression to disability. So the answer is till 1993 no fundamental disease-modifying therapy has been shown to work.

Q. And as of 1994, of the treatments that we've mentioned today, which of those were available for prescription?

A. Repeat that if you would.

Q. As of 1994, which of the various disease-modifying

therapies that we discussed today were available for prescription?

A. Betaseron was the only one.

Q. As of that time was there a long-felt needed for additional therapies for RRMS?

A. I think so, yes.

Q. Have you helped prepare a slide that sets forth what you think those needs were?

A. Yes, I have.

Q. Let's put that up. Slide number 14. Dr. Lisak, if you would just describe what you have set forth in this slide?

A. First bullet is that we needed another effective treatment for RRMS patients. The second is that we needed an effective treatment that worked differently than the available agent, the interferon beta 1, and we needed effective therapy that would have more tolerability and certainly less in the way of significant side effects, serious side effects.

Q. If we could just focus on the first bullet point, what do you mean by there was a need for another effective treatment for RRMS?

A. Well, as I testified earlier, beta interferon, Betaseron and the others don't effectively treat all patients with MS, relapsing remitting MS, so you have a population of patients who didn't benefit from the one available therapy. You needed one that worked differently, so the interferons work the same,

Copaxone works differently, so you have a patient whose MS needs a different way of modulating the immune system and that provides maybe what we call neuroprotection as well, that that would be a need, and we also need one that would work on a patient on interferon who might develop the neutralizing antibodies and interferon that worked for them for a while might not work any more so you need something else.

Then interferon has some tolerability issues, but it does have also the side effects of abnormal liver function tests and some bone marrow supression, so you need a drug for a patient who might be on interferon who might be doing well from the point of view of their MS but having a particularly significant side effect such as abnormal liver function or bone marrow supression so you need something else.

Q. Did these needs that you're referring to continue to exist as of 1996 when Copaxone was introduced?

A. Yes, because the only other drug after Betaseron and Avonex is interferon.

Q. Did the introduction of Copaxone meet these needs, sir?

A. I believe they did.

Q. Could you explain how that happened?

A. Copaxone works, is effective, it works differently on the immune system and it has no bone marrow supression, no flu-like illness and no liver function test abnormalities and doesn't require -- because it doesn't have flu-like -- for you to treat

the patient prophylactically every time you inject them with medicines that you would take if you had the flu. So it's much simpler to use.

Q. Have you seen Copaxone fulfill these needs in your own practice?

A. Yes, I have.

Q. Could you just explain what you've experienced in your own practice, sir?

A. Well, in my own practice I have patients who I put on Copaxone who are doing very well. No lab problems to worry about, large percentage have not have any relapses, their neurologic exam doesn't show any changes over the years. Their MRI scan when we check it doesn't show many if any new lesions that we can see.

I have patients who I've treated or have been sent to me for second opinion who are no longer responding to interferon or can't take interferon because they just can't handle flu side effects or every time they get a dose, effective dose of interferon the liver has abnormal functions so I have made my patients and patients I have seen for other physicians switch to Copaxone in those patients and they continue to do well in their MS and don't have the flu or liver function or bone marrow problems, most of them don't have increased P or increase or onset of depression or stiffness or spacicity from it.

Q. Have any clinical studies been performed to show that Copaxone may be effective for patients for whom the interferons don't work?
A. Yes, there have been.
Q. What do those studies show generally?
A. Generally those studies show that patients who could not respond to or could not tolerate the side effects or tolerability issues of the interferons that a significant number of them tolerated Copaxone and did well as far as their MS is concerned.
Q. Have you prepared a few slides that describe those studies, sir?
A. Yes, I have.
Q. Let's move to slide 15 if we could. This is marked as PTX667 in your binder as well. Dr. Lisak, could you explain for the Court what we're seeing here?
A. This is a group of patients who were on interferon, I believe they were on beta 1A once a week, so that's Avonex, and they either did not tolerate the drug, they didn't want to inject anymore, or they had abnormal liver function tests or some other side effect or they were having relapses on Avonex and the patients were switched to Copaxone, that is the non interferon, and a large number of them did well and they all tolerated the drug and didn't have those side effects.
Q. Are you one of the co-authors on this article, sir?

A. Yes, I am.

MR. BENNETT: Plaintiffs move for the admission of PTX667, your Honor.

MR. DOYLE: No objection.

MS. BLOODWORTH: No objection.

THE COURT: All right. Admitted.

(Plaintiff's Exhibit PTX 667 received in evidence)

Q. Let's move on to side number 16, Dr. Lisak. Again, could you describe what's depicted here?

A. This is a study of glatiramer acetate Copaxone in a group of patients, some of whom have never been treated with anything yet for their MS, and others who have been treated with Betaseron, that's interferon beta 1B is Betaseron, and this studied patients who were naive, as well as on Copaxone, well tolerated, no side effects, and patients who for various reasons stopped taking their interferon, again either increased relapse or not tolerating or significant side effects, and most patients who were switched, many of them did well on the Copaxone.

Q. This is marked as PTX671 in your binder, Dr. Lisak and plaintiffs move for its admission.

MR. DOYLE: No objection, your Honor.

MS. BLOODWORTH: No objection.

THE COURT: Admitted.

(Plaintiff's Exhibit PTX 671 received in evidence)

Q. Doctor Lisak, does Copaxone continue to meet any of those long-felt needs that we discussed earlier?
A. I believe so, yes.
Q. And could you just explain what the basis is for your opinion on that?
A. Well, I have a large number of patients on Copaxone, either as their first therapy or as a switch to Copaxone. And a lot of our patients in our MS group clinic are also on the agent that seem to be doing well from my clinical experience based on a lot of years and a lot of patients and all the prospective long term studies continue to show well tolerated, no significant side effects, and it continues to be efficacious for a large number of patients.
Q. Okay, Dr. Lisak, I'd like to switch gears and focus on the opinion that you mentioned at the outset of your testimony regarding the failure of others. I believe you mentioned earlier that a number of potential treatments for MS have failed. Could you just explain for us what you mean by a treatment failing?
A. Treatment failure would be either it didn't benefit the MS, they've had relapses, didn't improve the patients, they had progression or it was toxic, not tolerated, and sometimes it's actually made the MS worse, so those would be three ways of a drug development failing, agent failed.
THE COURT: What was it you said, what was the last

one, it may be what?

THE WITNESS: Actually worsen the MS itself.

THE COURT: Got you.

Q. When have these failed attempts occurred?

A. Since 1864, probably, but certainly in the modern era since the 1960's on, that I'm aware of, or at least since I was in medicine.

Q. Have you helped prepare a slide that summarizes some of the more recent failed attempts?

A. Yes, some of the more recent.

Q. Let's put up slide number 17. Dr. Lisak, can you explain what we're seeing here?

A. Across the top what you have is the first column treatment, treatment is listed below, subcategorized, the company that was involved, when there was a company involved, the approximate dates when the studies were being done and then why they are considered a failure.

So if we start at the top, Isoprinosine tested in the early 1980's and did not improve the patient disability. Prednisone, which its variants are used for acute attacks did not improve disability or did not reduce or delay attacks. The transfer factor, which is a material obtained from the white cells of normal individuals and given to the patients did not benefit the patients.

The next group are called immunosuppressants. Immuno

modulating suppressant therapy. Roquinimex in the 1990s was worked on by Pharmacia-Upjohn and Phase II studies were actually cut short because there was significant side effects including death and myocardial infarctions and heart attacks.

Gusperimus, another antibiotic immunosuppressant from Bristol Meyers Squibb, around a little bit earlier, did not seem to provide any benefit. Sulfasalazine, Pharmacia Upjohn that's a drug used in inflammatory bowel disease, like Crohn's and colitis did not have effects over the three years. Interestingly, in about a year it looked promising, but when we took the study out three years it turned out not to be effective.

Then Cladribine, it's a chemotherapy drug used for certain kinds of leukemia, Merck, that's been turned down twice by the FDA and once by the European Union's equivalent of the FDA, because of side effects and the FDA on the last occasion asked the developing company to essentially do additional safety studies and I believe that the company has decided not to go forward with that with the FDA or the European Union. So that one, whether it worked or not was simply unacceptable toxicities.

Q. Could we just move on to the next slide, 18?

A. Okay, so something we called cytokine modulators. I mentioned that the inflammatory autoimmune and other cells secrete different things and one of the things they secrete are

cytokines. That's it briefly.

Lenercept is a drug that's actually used in rheumatoid arthritis and psoriatic arthritis and that was tested in MS and it no only failed to produce efficacy, but actually some patients worsened. They had more attacks and more active MRI lesions.

Infliximab, which works sort of a different way on the same system, is a product of Centocor. That did the same thing as Lenercept. It didn't work and some MS patients actually got worse.

TGF beta 2, I apologize, but it has no brand name, is a cytokine itself that's supposed to beat down the regulatory immune system and that did not seem to work in the clinical trial.

Then people have tried what we call antigen-derived therapies, that is trying to test things that look like parts of a myelin, desensitizing, if you will -- a gross oversimplification of how it would work, but oral bovine myelin was tried. That didn't work. That was a Phase III double blind placebo-controlled trial and the patients who received the medicine did no better than the placebo patient.

Then Tiplimotide from Novartis from the early 2000's actually seemed to worsen some patients so a little like the Lenercept and Infliximab, actually didn't seem to help but actually seemed to worsen some patients.

Q. Please move to slide number 19 and what do you see here, Dr. Lisak?

A. These are three of the monoclonal antibodies that have been tried in MS that did not make it. Failed. The one Muromonab CD3 from Ortho caused significant toxicity, so it couldn't be used, and Priliximab, which is again another series of lymphocytes, inflammatory cells, from Centocor was ineffective in Phase II trials, so Phase III was not done.

Threaten Antova from Biogen was stopped because it was being tested in several auto immune diseases and patients were developing clots including deep vein thrombosis, so this was never fully tested in any of those. They just stopped those studies. So these were some of the more recent ones.

Q. And these exhibit numbers are representing slides, sir? What are they representing?

A. Those are actually the reports or papers or abstracts where each of these individual agents were presented at meetings and so forth.

MR. BENNETT: Your Honor, we'll offer those into evidence at the conclusion of Dr. Lisak's testimony today.

THE COURT: All right.

Q. As a clinician, sir, what do these failed efforts at develop MS treatments mean to you?

A. It means that it's difficult to develop therapies for multiple sclerosis, to find something that works, that patients

follow and that has a regular safety profile for patients with that particular disease.

Q. Why is it difficult to develop these drugs, sir?

A. Multiple sclerosis is an unpredictable disease. You need large controlled studies. The immune system and the nervous system are, I would put forth, are the two most complex systems in the body and you're seeing an interaction of those two systems and it's not easy to get an effective therapy that's also safe and tolerated by people who are young, so that's the issue. The issues.

Q. What do these failed attempts tell you about Copaxone?

A. That it was a significant step in the treatment of patients with multiple sclerosis because it is effective, it has a reasonable side effect profile that most patients seem to do well with, and it has no significant and certainly no major safety side effects and has been shown over sustained use both in clinical practice and in the prospective followup of the original Johnson trial that it continues to work and be safe so it seems to me that's significant.

Q. What has the introduction of Copaxone meant to you and your patients?

A. It means I have something to offer patients that seems to work well for them, and it gives me something to offer patients who have tried other agents that they either don't find effective or that they don't tolerate or they develop a side

effect and they just can't continue with it, such as bone marrow supression or intolerable flu every time or liver function abnormalities.

Q. I'd like to switch topics again and turn to the infringement that I mentioned at the outset of your testimony. Did you compare defendant's proposed generic products with any claimed limitations of the patents at issue in this case?

A. Yes, I did.

Q. What type of claim limitations were you asked to consider?

A. I was asked to consider some claim limitations that are in the prescribed -- proposed prescribing information for the Sandoz and Mylan product and compare them to the similar parts of the Copaxone.

Q. Were the claim limitations that you asked, that you were asked to look at in the patents in suit?

A. Yes, they were.

Q. And you compared those limitations to the defendant's proposed products, right?

A. That's correct.

Q. If we could pull up slide number 20, Dr. Lisak. Just describe what we are seeing here.

A. First column is the patent number, second is the claim, number of the claim, and then the limitation, and then you have the Sandoz product and the Mylan product in the last two columns.

Q. What did you do to determine whether Sandoz and Mylan's proposed generic products met these claim limitations?

A. I looked at the proposed prescribing information, drug label, which is a term I like to use for the proposed Sandoz and the proposed Mylan product and I compared it to the identical parts of the Copaxone prescribing information.

(Continued next page)

BY MR. BENNETT:

Q. As a prescribing physician, how do you use labeling information?

A. You use that to determine which patient should be treated with the medication, what the dose and frequency and route should be, as well as what safety side effects to consider.

Q. What is information concerning the use of a product referred to on a pharmaceutical label?

A. Use would be -- well, there's recommended route, frequency, and dose are the key things.

Q. Is that information referred to as the indications and usage?

A. That would be the indications and uses of any drug that's has a labeling information, product information.

Q. Are you familiar with the approved labeling for Copaxone?

A. Yes, I am.

Q. Okay. I'd like you to turn to tab PTX-697 in your binder. This is an exhibit that was admitted with Mr. Congleton this morning.

A. Okay, I have it.

Q. Dr. Lisak, do you recognize this document?

A. Yes, I do.

Q. What is it?

A. It's the prescribing information for Copaxone.

Q. Okay. And I first like you to direct your attention to the

bottom right-hand corner of the top half of this page, if that makes sense?

A. Yes, I understand.

Q. Do you see a date depicted there?

A. Yes. February of 2009.

Q. What does that date mean?

A. That means that that is the date of the FDA approval of this particular document.

Q. Is this the current labeling for Copaxone?

A. Yes, I believe it is.

Q. Okay. Now, if we could turn to the second page of this document, sir, and focus on the top left-hand portion?

A. Okay.

Q. Do you see a reference there to the active ingredient of Copaxone?

A. Yes.

Q. What is that, sir?

A. Glatiramer acetate.

Q. Okay. And focusing in on section one of the labeling, what information is set forth in the indications and usage section?

A. So the indications and usage is what you're supposed to use it for and who should use it on.

So it's to be used for reduction of frequency of relapses in patients with relapsing-remitting MS or RRMS including, patients who have first clinical episode and MRI

features consistent with MS. So that's the so-called clinically isolated syndrome that I mentioned this morning.

Q. Have you prescribed Copaxone yourself for these uses, sir?

A. Yes, I have.

Q. What is the dose of Copaxone you have prescribed patients?

A. The dose, which is the next section down, is 20 milligrams a day, it's by injection. It's to be injected under the skin subcutaneous, and is not to be administered into a vein intravenously.

Q. That 20-milligram per day dose that you're referring to is reflected in section two?

A. 2.1.

Q. Thank you. Dr. Lisak, I'd like you to turn to tab PTX-206 in your binder back at the beginning.

A. Yes, I see it.

Q. Do you recognize this document, sir?

A. Yes, I do.

Q. What is it?

A. This is the draft label and text for the draft package insert or prescribing information, whichever term you choose to use, by Sandoz.

Q. Okay. So is this the proposed labeling for Sandoz's proposed product?

A. That's how it's identified.

Q. Okay. Let's turn to the Bates ending in number 34, if you

would.

A. I don't see the -- this copy seems to be stuck. Let me see if I can find it.

Q. Sorry, sir. I'm referring to page four of 24?

A. Okay.

Q. And focusing on the indications and --

A. Just opening -- somebody in putting the sticky stuck them together. I have it now.

Q. Focusing on the indications and usage section, what information is set forth here?

A. It tells you what the agent is and what it's supposed to be used for.

Q. And what does it state, sir?

A. It says the glatiramer acetate injections indicated for reduction of the frequency of relapses in patients with relapsing remitting multiple sclerosis.

Q. How does that statement compare with the approved labeling for Copaxone?

A. It's the same as far as treating RRMS, same thing.

Q. If Sandoz proposed product is approved with this label, how would a prescribing physician interpret this indication and usage information?

A. They would interpret that the Sandoz product is to be used to reduce relapse frequency in patients with RRMS.

Q. And if we could move forward, I'll just find the page

number, the Bates has been taken off, move forward to page 14 of 24, sir?

A. Okay.

Q. And focusing on the dosage and administration section?

A. Okay.

Q. What does that information set forth?

A. It says that the recommended dose of glatiramer acetate injection for the treatment of RRMS is 20 milligrams per day injected subcutaneously.

Q. How is that information compared to the dosage information in the Copaxone labeling?

A. It's the same.

Q. I'd like you to turn to tab PTX-734 in your binder, sir.

MR. BENNETT: While we're doing that, your Honor, plaintiffs would move for the admission of PTX-206?

THE COURT: Any objection?

MR. DOYLE: None.

THE COURT: Admitted.

(Plaintiff's Exhibit PTX-206 received in evidence)

A. I have 734.

Q. Okay. Do you recognize this document, sir?

A. Yes, I do.

Q. What is it?

A. This is the proposed prescribing information for the Mylan product.

Q. If we could turn to page ending with the Bates number 949?
A. Okay.
Q. I'd like to direct your attention to the section entitled, indications and usage. What information is set forth in that section of Mylan's proposed label?
A. It's says that glatiramer acetate injections indicated for reduction of frequency of relapses in patients with relapsing remitting MS, RRMS, including patients who have experienced first clinical episode and have MRI features consistent with multiple sclerosis -- again that later refers to the so-called clinically isolated syndrome patient.
Q. How does this information compare with the labeling for the Copaxone?
A. It's identical.
Q. And again if Mylan's propose product is approved with this label, how would a prescribing physician interpret this in the indication and usage information?
A. They would interpret it as saying that you could use, you can use this agent to treat RRMS patients or the CIS patients to reduce the frequency of their relapses.
Q. And moving down to the dosage and administration section, specifically section 2.1.

Doctor, what information is set forth in this portion of Mylan's proposed labeling?
A. 2.2, recommended dose says the glatiramer acetate injection

is for subcutaneous use only; do not administer intravenously. The recommend recommended dose of glatiramer acetate is 20 milligrams a day.

Q. How is that information compared to the dosage information on Copaxone label?

A. It's the same.

MR. BENNETT: Plaintiffs move for the admission of PTX-734, your Honor?

MS. BLOODWORTH: No objection.

THE COURT: All right, 734 is admitted.

(Plaintiff's Exhibit 734 received in evidence)

Q. Dr. Lisak, did you help prepare a slide that summarizes your opinions on infringement?

A. Yes, I have.

Q. Let's take a look at slide number 20. And again, Doctor, this is listing the claim limitations that you're opining on, sir?

A. Yes.

Q. All right.

A. Patent and claim.

Q. Dr. Lisak, in your opinion, if Santos and Mylan's proposed product are approved by the FDA, would there use come -- Dr. Lisak, in your opinion, if Sandoz and Mylan's proposed products are approved by the FDA, would their use comprise a method of treating multiple sclerosis?

A. Yes, they would.
Q. If Sandoz and Mylan's proposed products are approved by the FDA, would their use involvement administering to a subject neither of a pharmaceutically effective amount of the active ingredient?
A. Yes to both parts of that.
Q. If Sandoz and Mylan's proposed products are approved by the FDA, would they be compositions for the treatment of multiple sclerosis?
A. If FDA approved, they would be.
Q. And, again would those proposed products contain a pharmaceutically effective amount of the active ingredient?
A. Again, if approved, yes.
Q. Now moving to the limitation of '539 patent, sir. If Sandoz and Mylan products were to be approved by the FDA, would they be suitable for treating multiple sclerosis?
A. Yes.
Q. And, in your opinion, if Sandoz and Mylan's proposed products would be approved by the FDA, would they contain a dose of active ingredient therapeutically effective to treat multiple sclerosis?
A. Yes, if approved that's what they would be.
Q. If Sandoz and Mylan's proposed products are approved, would their prescription use be a method for treating in patients suffering from multiple sclerosis?

A. Yes.
Q. And, Dr. Lisak, if Sandoz and Mylan's proposed products are approved by the FDA, will there use comprise administering the active ingredient to a patient thereof?
A. Yes, that's what it would be.
Q. And finally with reference to the '098 patent, sir. If Santos and Mylan proposed products are approved by the FDA, would they be suitable for treating multiple sclerosis?
A. Yes, they would be.
Q. Again, Dr. Lisak, what are your infringement opinions based on?
A. They're based on comparing the documents that we just discussed, and my experience as someone who has been treating patients with multiple sclerosis as a staff attending neurologist since 1972, and as a resident even before that.
Q. In your opinion, will the proposed labeling for Sandoz and Mylan proposed products encourage physicians to use their products to treat patients with multiple sclerosis?
A. Yes, it would.
Q. Thank you, Dr. Lisak.
MR. BENNETT: We have nothing further, your Honor.
THE COURT: All right. Thank you, Mr. Bennett. Cross-examination.
MS. BLOODWORTH: Yes, your Honor. Thank you.
THE COURT: Ms. Bloodworth.

CROSS EXAMINATION

BY MS. BLOODWORTH:

MS. BLOODWORTH: Everyone's ready?

THE COURT: Go ahead.

Q. Thank you, your Honor.

Dr. Lisak, my name is Shannon Bloodworth and I represent the Mylan and Natco defendants. And you should have a binder in front of you that should help you with the materials today.

A. I do. Thank you.

Q. Now, you testified during your direct that you were one of the lead investigators on the Johnson trial, correct?

A. I testified I was one of the investigators on the Johnson trial.

Q. You were the director of the Wayne State Center?

A. That is correct.

Q. And you co-authored the study to the publish results of the Johnson trial, correct?

A. That is correct.

Q. You could turn to PTX-597 in your binder, please.

MS. BLOODWORTH: Your Honor, I'm going to approach. We have a technical -- we have to switch the signal, apparently.

THE COURT: Oh, sure. Come on up.

Q. Sorry for the interruption, Dr. Lisak.

A. No problem.
Q. Now, no one knew the results of the Johnson trial, I believe you testified, until the end of 1994, is that correct?
A. That's when the presentation was made in a national meeting, that's correct.
Q. So none of the results of the Johnson trial are reported in the patents in suit, correct?
A. I don't know that I can answer that having examined all of the patents in suit.
Q. Okay. The specification, the background is the same for all nine patents in suit, I'll make that representation to you, but I can show you PTX-1 if you like to look at the '808 patent?
A. But I -- no. But I'm saying I only examined the parts that I was asked to look at the patents in suit.
Q. Okay.
A. So I have no idea what's in any other part of it.
Q. Okay. Are you aware that the Bornstein 1987 study is reported in the patents in suit?
A. I've been told that they were.
Q. Are you aware that the patents in suit were filed in May of 1994?
A. I knew sometime in 1994. I didn't know exactly when.
Q. Okay. Now, as one of the directors of the Wayne State Center for the Johnson trial, you were aware of the primary

outcomes for the trial, correct?
A. Yes.
Q. And was one of the primary outcomes of the Johnson trial to establish that lower molecular weight co-polymer-1 reduced injection site reaction?
A. Not to my knowledge.
Q. And was any of the end points in the 1995 Johnson trial to establish the efficacacy of a lower molecular weight co-polymer-1?
A. The purpose was to study the efficacy of the material that we were testing, which is the material in this paper.
Q. And if you look at PTX-597 on the page ending 1269?
A. Yes.
Q. In the left-hand column the materials you were testing is co-polymer-1 with an average molecular weight of 4700 to 13,000 daltons; is that correct?
A. That is correct.
Q. And the molar fraction of the material you were studying is a molar ratio of 4.2 to 1.4 to 3.4 to one, correct?
A. I don't know about molar fraction. I know what it says about the molar ratio.
Q. And you're a co-author of this paper, right?
A. Yes, I am.
Q. Now, you're aware, though, that currently Copaxone is approved with an average molecular weight of five to 9,000

daltons, correct?
A. That's what's listed on the most recent approved FDA document, that's correct.
Q. Okay. That you were just reviewing with Mr. Bennett?
A. That's the one.
Q. Okay. And I believe for the record that's PTX-697?
A. Yes. I think Mr. Congleton also was asked about that.
Q. And you mentioned that the only difference between the Johnson 1995 trial and the Bornstein 1987 trial was the difference in the average molecular weights?
A. I didn't say that.
Q. Do you know if that's the only difference between the copolymers between the 1987 Bornstein study and the 1995 Johnson trial?
A. You asked me if there were differences between the study.
Q. If there was -- excuse me, let me strike the question.

I believe you testified on your direct that the only difference in the co-polymer-1 that was studied between the 1987 Bornstein and the 1995 was the difference in average molecular weight?
A. No, I did not recall saying that. I don't think I was asked about the molar ratio. I must have been -- I could look again, but I don't recall that question.
Q. Okay. My question was to the average molecular weight, sir?

A. The average molecular weights are different, not the -- I don't believe I discussed the molar ratio.

Q. Okay. If we can, if you can turn to PTX-31 in your book, please?

A. 31?

Q. 31, sir.

A. Any particular order?

Q. I think they're typically DTX before PTX.

A. Okay. And you said this was which?

Q. 31, P, as in Paul?

A. P, okay.

THE COURT: This is not yet in evidence, is that right?

MS. BLOODWORTH: PTX-31 is in evidence from the July trial, your Honor.

A. I got --

THE COURT: Oh, the first?

MS. BLOODWORTH: The first phase, but --

THE COURT: That's fine.

A. I have it.

Q. Okay.

THE COURT: Could you just indicate that as we go along.

MR. HASHMALL: Sure, your Honor.

THE COURT: All right.

Q. And we can also -- looking at PTX-31, do you recognize this as the 1987 Bornstein trial?
A. That's the paper that describes the trial, that's correct.
Q. Okay.
MS. BLOODWORTH: I officially move it into evidence as well, your Honor.
THE COURT: All right, it's admitted.
(Plaintiff's Exhibit PTX-31 received in evidence)
Q. And if you turn to the second page of the exhibit -- actually, I'm sorry, the first column on the first page on the left-hand side. Actually it's going to be pulled up on the screen. It reports a molar ratio of six to 1.9 to 4.7 to one, correct?
A. 6 to 1.94 -- that is correct.
Q. And those are different numbers than what was reported in the Johnson '95 trial, correct?
A. The numbers are not the same.
Q. Thank you. And also I believe you testified that you didn't think this was a -- that this the 1987 Bornstein trial approved efficacy of co-polymer-1, is that correct?
A. I don't consider it proving it evidence.
Q. And you had two bases for your opinion, one was that it was a small number of patients and the second was that it was not blinded, is that correct?
A. It was not double blinded, that's correct.

Q. If you can look at the first paragraph, the second -- the second paragraph in the study. It actually does report that it was a double blind study, correct?
A. That's what it says.
Q. Now, you also testified that the first time co-polymer-1 was made available to patients was after the Johnson trial, correct?
A. I testified that it was made available, I believe we said in 1997, I believe.
Q. And you're also aware that co-polymer-1 was made available through the, through two other trials by patients, I mean by the FDA, correct?
A. You'd have to tell me what you're referring to.
Q. Sure. Are you aware that the FDA approved Dr. Murray Bornstein to administer co-polymer-1 to patients in 1986?
A. I've became aware of that during preparation for this trial, but did not know so at the time of the study.
Q. And it's your opinion that Copaxone alone met that need, correct?
A. Yes.
Q. And what about co-polymer-1, did co-polymer-1 also fill that long unfelt need?
A. Are you referring to co-polymer-1 as the material in the Bornstein study?
Q. Yes, sir.

A. Okay. The answer is no, did not.
Q. And you know that the FDA approved Teva to -- for a treatment IND in 1993 to administer co-polymer-1 to patients, correct?
A. I believe I knew that there was going to be some treatment IND during the latter stages of the Johnson trial, and I have no details of it.
Q. Did you ask to see that protocol for your report?
A. That one, no.
Q. Did you ask to see the Dr. Bornstein's compassionate use materials in preparing your report?
A. I have seen it.
Q. You can turn to D, as in David --
A. Got it.
Q. -- TX-1303 in your binder, please?
A. 13 -- could you repeat that again?
Q. Sure. 1303.
A. Got it.
Q. And that is letter to the FDA from Dr. Bornstein, dated June 16th, 1986; you see that?
A. Yes. It's signed by Dr. Bornstein.
Q. And he is requesting a -- first paragraph says, he is requesting a claimed exception to obtain a compassionate investigation new drug application?
A. Compassionate.

MR. HASHMALL: Your Honor, I'm going to object to this line of questioning. I don't think any foundation is laid he's actually seen this document before.

MS. BLOODWORTH: Your Honor, I was trying to lay the foundation. He said he was aware of Dr. Bornstein's compassionate use study, was going to familiarize himself, Dr. Lisak with the document and see if this was what he was recalling?

THE COURT: Well, you can just take a look at the document and --

A. Okay.

THE COURT: -- Doctor, and let us know if this is what you remember, if it refreshes your recollection I guess.

A. Yeah. I, as I said, I only saw it in preparing for the trial. I never seen it before then, and I've only seen it briefly, once.

Q. Okay. So if I understand your direct testimony correctly, you're drawing a distinction between copaxone and co-polymer-1, is that correct?

A. I'm drawing a distinction between what you asked, which is what Dr. Bornstein published in '87, and what Dr. Johnson and the rest of us studied in '91 through '93, '94.

Q. And if I could turn your attention to, in your binder, to DTX-1920. Do you regularly review the Anals of Neurology as part of your business practices?

A. I read it, yes.
Q. This is an article in that journal entitled Expanded Clinical Trials of treatments for multiple sclerosis?
A. It's a letter to the editor, actually.
Q. Letter?
A. Not a peer reviewed article.
Q. And it's by Dr. Yafit Stark?
A. That is correct.
Q. Do you know who Dr. stark is?
A. Yes, I do.
Q. Who is Dr. Stark?
A. She's an employee of Teva Pharmaceuticals.
Q. This article is dated July 1994?
A. This letter is dated.
Q. Letter, thank you. Letter dated July 1994. At the bottom?
A. That's when was it was published, yeah, July issue.
Q. And in this it references Dr. Stark is writing about the treatment IND protocol?
A. Apparently in response, as letters to the editor often are, to an earlier article or review or something by another, another author, so that we don't have that particular article here that she's referring to by a Dr. John Whitaker I gather from looking quickly at this letter.
Q. And it says, the treatment IND was approved by the FDA in January of 1993; you see that?

A. Yes, it says that.
Q. Does that refresh your recollection as to when the treatment IND was approved?
A. Yes, it was, as I said, late in the trial, in the period of Johnson trial.
Q. So you're aware of two other ways patients could receive co-polymer-1 prior to 1996, Dr. Bornstein's compassionate use program, and the treatment IND, correct?
A. A limited number of patients could receive this as part of a treatment compassionate use IND study.
Q. And if we could in fact take you back to your labeling, the labeling that was looked at PTX, I believe it was 697?
A. Okay.
Q. You can turn to section 14 of the labeling?
A. Okay.
Q. And in section 14 it refers to a study one. Do you see that on the bottom left-hand part of the 14.1?
A. I do. Yes, I do.
Q. Paragraph right under 14.1 one says that the evidence supporting the effectiveness of Copaxone in decreasing the frequency of relapses derives from three placebo controlled trials, all of which used Copaxone dose of 20 milligrams per day; see that?
A. Yes.
Q. And then it goes on to say that study one was performed in

a single center on 50 patients. Do you recognize that as the 1987 Bornstein study?

A. Yes, that would be what it would seem to be.

Q. So the current labeling is relying on the 1987 Bornstein data, correct?

A. It's included in there.

Q. And the next study, study two, and that's the Johnson 1995 study, correct?

A. Yes, study two; yes, it would appear to be.

Q. And right underneath table three in the labeling it concludes that in both studies Copaxone exhibited a clear beneficial effect on relapse rate and is based on this evidence that Copaxone is considered effective. You see that?

A. I see that.

Q. So in labeling they're relying on both the 1987 Bornstein and the Johnson trials to prove Copaxone's effectiveness, correct?

A. Means that the FDA has apparently considered both of those in their decision.

THE COURT: Ms. Bloodworth, I'm sorry to interrupt you. I have a very short matter, I want to take it in the courtroom next door. So we'll take a 15 minute break at this point.

MS. BLOODWORTH: Thank you, your Honor.

(Recess)

(In open court; after the recess)

THE DEPUTY CLERK: All rise.

THE COURT: Please be seated everybody.

All right, Ms. Bloodworth, you can proceed.

MS. BLOODWORTH: Thank you, your Honor.

Q. I think, Dr. Lisak, before the break we were looking at PTX-697.

A. Yes, yes.

Q. And we were on the section underneath table three?

A. I believe that's right.

Q. So in the current Copaxone label is relying on the 1987 Bornstein trial for efficacacy, correct?

A. The FDA is using that trial in their determination, yes.

Q. And who submits that trial for use?

THE COURT: Ms. Bloodworth, could you speak up a little bit? I'm just having trouble hearing you.

MS. BLOODWORTH: Sure.

THE COURT: Could be me.

Q. And Teva submits the labeling to the FDA for approval, correct?

A. That is correct. As I understand it.

Q. And the Johnson trial, the average molecular weight of the co-polymer-1 was 4.7 to 13 kilodaltons, correct?

A. That's correct.

Q. And the PTX-697, the current labeling is from five to nine

kilodaltons, is that correct?

A. That is correct.

Q. Let's look at the prior approved labeling of Copaxone that's in your binder at P, as in Paul TX-697?

A. Aren't we on 697? I'm sorry.

Q. Oh, excuse me. 695.

A. I have that.

MS. BLOODWORTH: And, your Honor, this was already admitted into evidence as well.

THE COURT: Thank you.

Q. And on the upper left-hand corner this says that the approved molecular weight range for Copaxone is 4.7 to 11,000 daltons, correct?

A. That's what it says.

Q. And if we turn to the right-hand column under table three again, excuse me, table two on the bottom left?

A. Okay.

Q. And there we also see in this labeling that in both studies glatiramer acetate exhibited a clear beneficial effect on relapse rate, and it is based on this evidence that glatiramer acetate is considered effective.

That is also based on the 1987 Bornstein data and the Johnson 1995 trial, correct?

A. Study one is the Bornstein study, two is the Johnson. So that would be correct.

Q. So Teva once again is relying on the Bornstein 1987 trial to prove efficacy of Copaxone?
A. It's using it, along with the Johnson trial it would appear.
Q. And it's using the Johnson trial and the Bornstein trial irrespective of the average molecular weights of co-polymer-1 used, correct?
A. I assume the FDA knew about the differences. So if they used them both, they're using them both.
Q. And you reviewed -- can you turn in your binder to PTX-1, please.
A. Okay.
Q. This is a copy of the '808 patent. You recognize this?
A. It says it's a copy of the '808 patent.
Q. And this is a patent that you reviewed in preparing your opinions here today?
A. I don't see the clinicals, so I'm not sure that I've actually either seen this or seen this part of it. I can't recall.
Q. Okay. Do you recognize the column one of the PTX-1?
A. I can read what it says.
Q. We're going to call it the '539 patent for you, which I believe is one of the patents that you opined upon. I just don't have it in your binder. I apologize.
A. Okay.

Q. DTX-1007, and if we can turn to the --
A. Is that in this binder?
Q. It's not in the binder. It's just up on the screen. Is it too small?
A. Yeah.
Q. Okay?
A. Unless I sit over there, maybe.
Q. If you can follow along?
THE COURT: Is it on your screen right there?
A. Now, it's large enough to see. Yes.
Q. Okay. It says 539 in the upper right-hand corner?
A. Yes it does.
Q. Okay. And if you look at the -- we can just turn to the first column. And you'll see that it's a co-polymer-1 improvements in compositions of copolymers?
A. Yes, that's what it says.
Q. Okay. And if we turn to column three, please. And in column three it is example two. Have you reviewed example two before, Dr. Lisak?
A. I don't believe so. I don't recall it anyway.
Q. Have you, in your years of prescribing treatments for MS patients, have you ever prescribed Copaxone based on whether or not it was toxic in the RBL assay?
A. No.
MR. BENNETT: Your Honor, objection. Again I don't

see the relevance to this case, and do Dr. Lisak isn't here testifying about the examining models.

THE COURT: All right. Do you have more to do on this?

MS. BLOODWORTH: Your Honor, just a simple basic questions of whether or not Dr. Lisak has ever opined or made any of his treatment decisions based on any --

THE COURT: You asked, but ask him that and you can move on.

Q. And going to ask about the in vivo mass study in part B.

THE COURT: All right, I'll allow those two questions. Go ahead.

MS. BLOODWORTH: Thank you.

Q. Dr. Lisak, in your treatment decisions, have you ever relied upon the in vivo mouse studies for Copaxone?

A. In vivo, which vivo, these?

Q. Yes, in example two?

A. No, I've not.

Q. And have you ever distinguished in prescribing Copaxone between the Copaxone that was approved from 4.7 to 11 kilodaltons versus the Copaxone approved at five to nine?

A. I've prescribed whatever was available to my patients when I write the prescription.

Q. So in between 1996 and 2001 when the Copaxone label was approved from 4.7 to 11, did you see any less side effects than

the current Copaxone in your patients?
A. Unless you're doing a control study, I don't know how you can say that, so I you really can't answer that.
Q. Have you ever seen a controlled study such as that?
A. Such as what?
Q. Such as what you just referred to, that unless you have a controlled study comparing the two, you can't determine?
A. I don't know of any such study. If it's done, I've never seen it.
Q. And you talked a little bit in your direct examination about the mechanisms of action of the various treatments?
A. Yes, I did.
Q. The mechanism of action for Copaxone is unknown, is that correct?
A. I believe I said there were multiple mechanisms of action. Which ones are the most important at certain times is not known. So overall, we don't know the exact mechanism of action. We know some mechanisms of actions.
Q. And when you discuss mechanisms of action, you're discussing how the actual drug works in your body; is that correct?
A. How it works in the patient, that's correct.
Q. In the patient. You're not talking about how the actual amino acids in the co-polymer-1 composition provide its activity, correct?

A. Absolutely not. That's correct.

Q. Now, in slide 14 of your direct presentation -- can we pull that up?

You mentioned -- I believe you testified as to these three long felt needs in 1994 for MS therapy. Do you recall that testimony?

A. Yes, I do.

Q. Okay. Now, did co-polymer-1 meet the need for another effective treatment for RRMS?

A. Yes.

MR. BENNETT: Objection, your Honor. I'm not sure what the question's asking in terms of what co-polymer-1.

THE COURT: You'll be able to do redirect. If you don't understand the question, Doctor, just tell Ms. Bloodworth. Go ahead.

Q. So, and just to, just to make sure everybody's on the same page, want to be clear. Dr. Lisak, I'm referring to co-polymer-1 as opposed to Copaxone. So the Weissman co-polymer-1 that was developed in the 1970's, that was the study, the 1987 Bornstein study?

A. I don't believe that's what I was testifying to. I believe I was testifying to Copaxone.

Q. Okay. So my question is as to co-polymer-1. Is it your opinion that co-polymer-1 met the needs for another effective treatment for RRMS?

THE COURT: You want to redefine what you mean by co-polymer-1 and ask the question.

Q. Co-polymer-1 as it was developed by the Weissman scientists and was used in the 1987 Bornstein study?

A. I believe that one, but not referring to this slide, I said I didn't think to my mind it proved it.

Q. Okay. And in your mind did it, co-polymer-1 one meet the needs for an effective treatment that worked differently -- again drawing the distinction between co-polymer-1 and Copaxone?

A. If it's anything from the Bornstein trial, I review as a said as pilot and not definitive. So it would be -- would be still the same as the -- my answer to the first bullet point.

Q. And your answer would be the same for the third bullet point as well?

A. Yes.

Q. So your opinion is resting on the FDA approval of Copaxone, not the difference in the co-polymer-1 compositions themselves, is that correct?

A. No. I'm saying that my opinion is based on the study that I was involved with in, subsequent studies, because they're large enough to have the power to tell you whether it is effective and if it has -- what its side effect and tolerability profile is. And that my comment on the different mechanisms of action along the way, I guess that's sort of a

second bullet, is based on a vast literature of immunologic studies in patients and in animal model not related to toxicity of MS that shows that the agent works. But it's not related to just the Bornstein study.

Q. But you're not drawing a distinction between the composition of co-polymer-1 and Copaxone in your answer, is that correct?

A. I'm guess I'm not following you. I'm distinguishing between two studies that had multiple differences independent of the material that was tested in the Bornstein versus the Johnson, and subsequently the Comey studies and so forth.

Q. So is it your testimony today that the Weissman scientists did not -- let me put it this way. Is it your testimony that the Weissman study scientists failed to develop an effective MS treatment?

A. My testimony is that you could not make a definite conclusion about the material used by Dr. Bornstein. You could say it was or wasn't effective. I said you can't tell. I can't.

Q. Let's turn to a couple of the articles relied upon in your direct testimony. So that would be in your other binder, sir. And if you could turn to P, as in Paul TX --

THE COURT: What binder are we in?

MS. BLOODWORTH: We're in plaintiff's direct examination.

THE COURT: All right, that is?

MS. BLOODWORTH: PTX-667.

THE COURT: Okay.

A. 667, I have it.

Q. Okay. Now, sir, you relied upon this in your direct testimony, correct?

A. Yes, I did.

Q. And I believe you relied upon it to support that Copaxone was better than the interferon treatments, is that correct?

A. No, it's not what I said.

Q. What did you rely upon this for in your direct testimony?

A. That there was a need for drug, another drug that wasn't interferon, because patients who were not responding to one of the interferons, Avonex, or were having unacceptable side effects or tolerability issues did respond to Copaxone. That's exactly what the article says, and that's what I believe I said.

(Continued on next page)

Q. And in your opinion, does this article prove the effectiveness for that purpose?
A. It proves that this is an effective drug in patients who for some reason don't respond to or cannot continue to take interferon. It says what it says.
Q. But this study isn't a double blinded trial, is it?
A. This is not a pivotal trial that works better than placebo. This is a different type of trial, different type of study.
Q. It's observational, right?
A. Prospective but observational.
Q. Prospective and observational, correct?
A. This is both.
Q. If you could turn in your binder to P as in Paul TX671. And this is another article you relied upon in your direct testimony, correct, sir?
A. That's correct.
Q. And why did you rely upon this in your direct testimony?
A. Because this was another what we call switch study in part, that is, the patients, some were naive so they were never treated before, some were again for various reasons, interferon beta 1B which in the United States was sold as Betaseron were not tolerated or not effective and patients in those two categories seemed to respond to the agent they were given, Copaxone.
Q. But this study doesn't actually prove the efficacy of

Copaxone for that reason, does it?

A. It doesn't prove it compared to no placebo. It says that there are patients who observationally, in the switch patients observationally didn't tolerate or didn't do well on another drug and so having an alternative drug seemed to help those patients. So the switch part is what it is. The other is an open label prospective and I wasn't relying on that. I was relying on it for the switch part.

Q. And the switch part wasn't a double blinded pivotal trial, was it?

A. No, switch studies aren't.

Q. I believe you testified on your direct examination there were injection site reactions with Copaxone, is that correct?

A. That's correct.

Q. And that's still correct today, yes?

A. Yes, that's correct today.

Q. And it was correct in 2001 when were you treating patients with Copaxone?

A. I'm trying to get my dates straight. Yes.

Q. And it was correct also during the Johnson trial?

A. Yes, we reported that.

MS. BLOODWORTH: I have no further questions, your Honor. Thank you, Dr. Lisak.

THE WITNESS: You're welcome.

MR. DOYLE: Just some brief followup, your Honor.

THE COURT: All right, Mr. Doyle, go ahead.

CROSS-EXAMINATION

BY MR. DOYLE:

Q. Dr. Lisak, are you aware of any published articles in the scientific literature that address whether side effects associated with glatiramer acetate are connected in any way to the molecular weight of the treatment?

A. In patients?

Q. In patients.

A. Not that I'm aware of.

Q. Could you look again at PTX597, the publication of the Johnson study?

A. Give me a moment. I have it, thank you.

Q. This is the one on which you're listed as an author, correct?

A. That is correct.

Q. If you could turn to page 1274 and the first full paragraph in the left column.

A. Okay.

Q. Yes. And could you please, maybe we can catch up here, 597. There we go. The first full sentence, the difference in the mean relapse rate between groups in this study, although highly significant, was less pronounced than in the earlier copolymer-1 pilot study. So again just to orient us, by this study, you're talking about the Johnson study, right?

A. That is correct.
Q. And the pilot study, which was more pronounced, is Bornstein, correct?
A. Yes. Reference to the Bornstein paper in the New England Journal of Medicine, correct.
Q. So what's reported in your article is that the improvement in the relapse rate with lower molecular weight copolymer was not as pronounced as the improvement in the relapse rate seen with higher molecular weight copolymer, correct?
A. Given the proviso that you can't compare cross studies, that's what we saw.
Q. Thank you. Now, if you could turn just briefly one more time to the Copaxone product label, that's PTX697. And again, I'll be focusing --
A. If you could give me a moment, Mr. Doyle.
Q. Sure.
A. 697. Okay, I have it.
Q. And I'll be focusing again on section 14 dealing with clinical studies.
A. Okay.
Q. Are you there?
A. I'm there.
Q. Now, does section 14 state that there was any difference in side effects between study 1, the Bornstein study, and study 2, the Johnson study?

A. Let me look at the entire section 14, then.
Q. Sure.
A. Section 14 seems to deal only with efficacy results, as far as I could tell.
Q. And there's no distinction drawn in terms of side effects as between study 1 and study 2, correct? In that section?
A. That section doesn't deal with side effects in either study.
Q. Now, could we look, please, at the description of study 1 and what term is used by Teva there to refer to the copolymer-1 composition that was used in the Bornstein clinical trial? It's referred to is as Copaxone?
A. Yes, I'm following you. I'm just making sure I'm reading every paragraph. Okay, I've read it. Now, can you repeat your question?
Q. Yes. What term does Teva use in its product label to refer to the copolymer composition that's referenced here in study 1?
A. I do not believe I see any reference one way or the other.
Q. Well, isn't there a reference to doses of either Copaxone 20 milligram or placebo and Copaxone?
A. I guess I didn't understand your question, then. Could you repeat it one more time?
Q. Isn't it Copaxone that is the term used by Teva on its product label to refer to the copolymer-1 composition referenced in study 1?

A. Yes, the term Copaxone is being used in that.
Q. And likewise in study 2, your study, would you confirm that the term used for the copolymer-1 composition there is also Copaxone?
A. That's the term that's used, that's correct.
MR. DOYLE: Thank you. Nothing further.
THE COURT: All right.
MS. BLOODWORTH: Your Honor, if I may move into evidence two exhibits?
THE COURT: Okay.
MS. BLOODWORTH: It was DTX1920 and 1303.
THE COURT: I believe there was testimony about both. No objection, or any objection?
MR. BENNETT: Your Honor, with respect to 1303, that was the document --
THE COURT: Is that the letter? I don't remember.
MS. BLOODWORTH: That was Dr. Bornstein's document that he said he reviewed in preparation for his testimony.
MR. BENNETT: For what purpose is it being offered, may I ask?
MS. BLOODWORTH: It's being offered for the truth that copolymer-1 was available to patients prior to 1996.
THE COURT: I'm not sure that the doctor said any more than it refreshed his recollection. Did he say he reviewed it? I don't recall.

MS. BLOODWORTH: He did say he reviewed it as part of his direct testimony.

THE COURT: Why don't I ask, since you're sitting here, Doctor. Did you actually review that document? Do you see the one we're talking about?

THE WITNESS: This one, no, I don't believe this exact document, because I don't recognize, there's something in addition to that letter which I think has some of Dr. Bornstein's CV and I don't recall seeing that whole document, actually. There's another page after that page, your Honor, if you flip one more past that. Past Dr. Bornstein's signature there's some more. I have no knowledge of ever seeing this part of it at all, so I don't think I actually saw that one that I can recall, except just then. This one is different.

THE COURT: Okay. Then that won't be admitted for the truth. I'll review it in the context of the questions you asked him with respect to whether anything refreshed his recollection.

MS. BLOODWORTH: Thank you, your Honor.

(Defendant's Exhibits DTX 1920 and 1303 received in evidence)

THE COURT: Okay. Mr. Bennett, there were a couple of documents that were on your chart.

MR. BENNETT: Yes, your Honor. Thank you. Those are

PTX99, PTX523, PTX538, PTX591, 565, 605, 616, 617, 623, 626, 627 and 644 and plaintiffs would move for the admission of all of those into evidence.

THE COURT: I don't believe there were any objections as we went through these. Unless I hear one now, they're admitted. Yes, Mr. Doyle?

MR. DOYLE: Your Honor, just assuming that these are the published articles upon which this expert has relied.

THE COURT: That's what I believe they are.

MR. DOYLE: Thank you.

(Plaintiff's Exhibits PTX99, PTX523, PTX538, PTX591, 565, 605, 616, 617, 623, 626, 627 and 644 received in evidence)

THE COURT: Any redirect?

MR. BENNETT: No, your Honor.

THE COURT: Thank you, Dr. Lisak. You're excused.

(Witness excused)

THE COURT: Who is your next witness?

MR. JAMES: Plaintiffs call Dr. Gregory Grant.

THE COURT: All right, Dr. Grant.

MR. ACKER: Your Honor, I want to introduce myself, I'm Eric Acker and I'll be cross-examining Dr. Grant.

THE COURT: All right. I'm glad you did.

GREGORY GRANT,

called as a witness by the Plaintiff,

having been duly sworn, testified as follows:

DIRECT EXAMINATION

BY MR. JAMES:

Q. Good afternoon, Dr. Grant.

A. Good afternoon.

Q. Could you tell us where you reside?

A. I live in St. Louis, Missouri.

Q. Are you employed?

A. Yes, I am.

Q. By whom are you employed?

A. By the Washington University School of Medicine.

Q. What is your position there?

A. I am a professor of biochemistry of medicine and of developmental biology.

Q. Do you hold any other positions at Washington University, Dr. Grant?

A. Yes, I'm also the director of the protein and nucleic acid chemistry laboratories of Washington University.

Q. What is the protein and nucleic acid chemistry laboratory?

A. It's a laboratory that does studies for other scientists both inside and outside of the university.

Q. What types of researchers seek the assistance of your laboratory, Dr. Grant?

A. We have many different types of researchers. Some are just basic researchers looking at biochemistry questions. Some are researchers looking into investigation into diseases and some

are also physicians who actually treat patients.
Q. And what types of assistance do you offer them?
A. We do tests for them. Over the years, we've done many different types of tests. They include things like determining the molecular weights of proteins, determining the amino acid compositions of polypeptides and proteins, determining nucleic acid sequence of polypeptides. I've also synthesized polypeptides in the laboratory and right now we have a very large effort in DNA sequencing.
Q. How long have you been the professor of the protein and nucleic acid chemistry laboratory?
A. Next year it will be three years.
Q. Could you briefly summarize your educational background for the Court?
A. Yes. I went to Iowa State University, got my bachelors degree in biochemistry. From there I moved on to the University of Wisconsin Madison where I achieved my PhD in biochemistry. Then I moved on to St. Louis as a post doctoral fellow studying protein chemistry.
Q. What year did you receive your PhD?
A. 1975.
Q. What was the topic of your thesis?
A. It dealt with the study of proteins in blood clotting.
Q. Dr. Grant, you said you have a PhD in biochemistry? What is biochemistry?

A. Biochemistry is basically the study of chemistry that is found in the molecules of living organisms.
Q. Can you give us some examples of those kinds of molecules?
A. Yes. Examples are proteins, polypeptides, would include enzymes, those are the basic things that I study.
Q. What was the subject of your post doctoral research?
A. My post doctoral research studies characteristics or properties of various different proteins and enzymes.
Q. There's a lot of talk in this case about proteins and polypeptides. Could you tell us what the difference is between those two things?
A. Proteins are polypeptides.
Q. Could you explain that a little further? Why is that?
A. Because they're both made up of amino acids. Not all polypeptides are considered proteins, but all proteins are polypeptides.
Q. Why is it called a polypeptide?
A. It's called that because it's made up of amino acids that are joined together by bonds and poly simply means -- the bond is called a peptide bond. Poly simply means there are many of them.
Q. Is copolymer-1 made up of polypeptides?
A. Yes, it is.
Q. Now, as part of your post doctoral research, Dr. Grant, what in particular did you study about proteins?

A. I studied many aspects of proteins, but it included determining the amino acid composition, the sequence of proteins, and we also do quite a bit of work with determining the molecular weight using size exclusion chromatography a lot during that time.

Q. Since you completed your post doctoral research, Dr. Grant, what positions have you held?

A. After my post doc, I stayed on at Washington University as an assistant professor and then over the years I rose through the ranks through associate professor and then full professor.

Q. What year did you become a full professor?

A. 1995.

Q. Turn in -- let me get you some binders here, Dr. Grant, just one second.

MR. JAMES: For the record, your Honor, I've handed up two binders that have the under seal unredacted versions of the exhibits. The parties have worked together to try to come to some agreement on the confidentiality issues. I handed to Mr. Gomez a copy of the binder with public versions of the documents. If the documents ever become public we would ask that it would be those public redacted versions to be put in the public record.

MS. BLOODWORTH: Your Honor, if I may, this is Shannon Bloodworth for Mylan defendants. I believe our version of the documents are not in this binder, but we will be providing them

shortly.

THE COURT: What am I looking at?

MR. JAMES: You're looking at the unredacted version.

Q. Dr. Grant, could you turn in your binder to PTX760, please?

A. Okay.

Q. Can you identify that document, please?

A. Yes. It's a copy of my curriculum vitae.

Q. Is it reasonably accurate and up to date?

A. Yes, it is.

MR. JAMES: Your Honor, we would offer into evidence Plaintiff's Trial Exhibit 760.

MR. ACKER: No objection.

THE COURT: All right, admitted. Thank you Ms. Bloodworth.

(Plaintiff's Exhibit PTX 760 received in evidence)

Q. Dr. Grant, over the course of your career what has been the focus of your research?

A. The focus of my research has been almost exclusively on enzymes, proteins and polypeptides.

Q. What are enzymes?

A. Enzymes are proteins that carry out specific functions in the body. For instance, the proteins that help you digest your food are enzymes.

Q. And how many peer reviewed publications do you have?

A. I have over 120.

Q. And how many of these publications address protein chemistry?
A. Nearly all of them.
Q. Have you edited any books, Dr. Grant?
A. Yes, I have. I've edited a book called "Synthetic Peptides: A Users Guide," and for several years I was editor on Techniques of Protein Chemistry.
Q. Your book on synthetic peptides, what is the subject matter of that book?
A. A peptide is the same thing as a polypeptide and the subject of that book is the design, the synthesis, the study and analytical examination of polypeptides.
Q. What is a synthetic polypeptide?
A. A synthetic polypeptide is the same as a polypeptide that's made by a scientist in the laboratory.
Q. Do synthetic polypeptides have any relevance to the case we're here to talk about today?
A. Yes, they do. Copolymer-1 is a mixture of synthetic polypeptides.
Q. Dr. Grant, have you been active in any professional organizations?
A. Yes. I've been active in several organizations. The one I would point out is the Association of Biomolecular Resource Facilities. It's an international organization of scientists who are interested in developing methods for things like

determining the molecular weights of polypeptides, their amino acid compositions, their sequences and so forth.

Q. Have you held any leadership roles in that society?

A. Yes. I've been active on several committees in that society and I served as president of that society in 1993 and 1994.

Q. Have you served on any editorial boards for any journals?

A. Yes. I have also served on several editorial boards. Again, the one I think that I would point out is the journal of biological chemistry, which is the preeminent journal of biochemistry in the world.

Q. How does one get to serve on an editorial board, Dr. Grant?

A. You're invited by the executive editor of the journal, based upon your knowledge and your expertise.

Q. Have you served on any advisory committees for any governmental agencies?

A. Yes. I've been on several advisory committees for the National Institutes of Health.

Q. Can you tell us what you do when you serve on these advisory committees?

A. These advisory committees are called study sections and what we do is we receive grant applications from other scientists throughout the country and we look at them and try to evaluate them for their scientific merit, their scientific rigor and their worthiness for funding.

Q. What types of grant applications have you reviewed in the study sections that you participated in?
A. I reviewed the types of applications that meet my expertise, so almost all of them have dealt with some subject dealing with proteins or polypeptides or enzymes.
Q. Do you review grant applications having to do with the use of size exclusion chromatography?
A. Many of these applications will have that in them, yes.
Q. How many grants per year do you do when you're serving on a study section?
A. At the time I was doing it, I would say probably I review 40 or 50 grants a year.
Q. In addition to your duties at Washington University have you done any invited lectures?
A. Yes. I've done many invited lectures both in the United States and internationally.
Q. What do your lectures focus on?
A. Well, they can focus on various things, but mostly some of the lectures will be about my own research, while other of the lectures will be about the techniques that we use in the resource laboratory that I also direct.
Q. Have you taught any courses in your career?
A. Yes, I've taught courses to graduate students, they're graduate level courses. I mainly focus on proteins and polypeptides and I've taught large sections on how to study

them what the analytical techniques are and how to use them.
Q. What types of analytical techniques have you taught?
A. One that's relevant to this case of course is size exclusion chromatography.
Q. Could you tell us, what exactly is size exclusion chromatography?
A. Size exclusion chromatography is a method that allows you to separate proteins based upon their size, one from another, if they're all together in a mixture you can separate them so that they're not together any more. But it's also a method that allows you to determine their molecular weight.
Q. You said it allows you to separate proteins. Does it allow you to separate polypeptides as well?
A. Yes. I'm using proteins and polypeptides sort of interchangeably, but polypeptides certainly.
Q. What is the relevance of size exclusion chromatography to this case?
A. The relevance is that patents in suit list size exclusion chromatography as the method to use to determine the molecular weight of copolymer-1.
Q. Dr. Grant, are there different areas of size exclusion chromatography based on the purpose for which you're using the technique?
A. Yes. They're basically two areas, I guess. One is called, the focus on fractionation, which is simply the process of

training to separate one molecule from another, but in addition to that, there's a distinct other area that is analytical in nature, which is determining the molecular weight of those proteins, which uses size exclusion chromatography.

Q. Do you have experience with the use of SEC as an analytical tool?

A. Yes, I do.

Q. Now, a minute ago you mentioned fractionation. Could you explain to the Court what that means?

A. Fractionation is taking a mixture of things and separating them so they're no longer in mixture. In some instances you can actually purify them completely. The fractionation basically is trying to take a whole and divide it into fractions that contain different substances.

Q. Are there distinctions in SEC depending on the sample that you're analyzing?

A. Yes, there are. You can use SEC in an aqueous mode, by that I mean in water or a water-based solvent of some sort. SEC is also used with organic solvents. Which one you use really has a lot to do with the type of molecule that you're studying, and which one you use there are different interactions, so we say they're different ways the molecule will separate and different properties they will have in solution.

Q. Do you have experience with aqueous size exclusion

chromatography?

A. I have a lot of experience, yes.

Q. How long have you been doing aqueous size exclusion chromatography?

A. I've probably been doing that for 40 years or more.

Q. How many times would you say that you or someone under your supervision has performed aqueous size exclusion chromatography over the course of your career?

A. It would be hard to put a number on it, but certainly it's hundreds, might even be approaching thousands.

MR. JAMES: Your Honor, we would offer Dr. Grant as an expert in the characterization of proteins and polypeptides using size exclusion chromatography.

THE COURT: Any objection or voir dire?

MR. ACKER: Not at this time, your Honor, no.

THE COURT: All right, then I accept Dr. Grant as an expert in that field.

Q. Dr. Grant, did you put together a set of slides to accompany your testimony today?

A. Yes, I did.

Q. Let's put up the first slide. And Dr. Grant, could you explain to the Court the subject matters that you're going to testify about today?

A. Yes. This slide is just an overview of that, of those subject matters and I've grouped them into two categories. The

first is, there's a background on the technology that's mentioned in the patents in suit and that is the copolymer-1 production itself and the use of size exclusion chromatography to analyze it, to determine its molecular weight. And then the second is the application of the claims to the defendants' ANDA products and I'm going to compare the ANDA products with the molecular weight claim terms that are in the patents.

Q. Thank you, Dr. Grant. Could you turn in your binder to Plaintiff's Trial Exhibit 1?

A. Okay.

Q. Do you recognize that to be a copy of the 808 patent?

A. Yes I do.

MR. JAMES: Your Honor, the patents in suit have been admitted in the July trial.

THE COURT: Yes, they're all in.

Q. Now, Dr. Grant, can you tell me the date that the application was first filed for the patents in suit?

A. That's May 24, 1994.

Q. And do you have an understanding of the level of skill in the art in this case?

A. Yes, I believe it to be high level.

Q. Let's look at the next slide. Dr. Grant, could you explain what's shown in this slide?

A. Yes. This is my definition of a person with skill in the art. They're a person that needs to have an advanced degree or

something very equivalent to that in a chemical or biological discipline and they need to have significant experience in the synthesis or characterization of polymers and certainly in the proteins or synthetic peptides. In addition to that, the person would have access to other scientists who have expertise in those areas.

Q. Dr. Grant, did you analyze the patents in suit from the point of view of a person of ordinary skill in the art in 1994?

A. Yes, I did.

Q. Were you a person with ordinary skill in the art in 1994?

A. I was.

Q. Dr. Grant what is the general subject matter of the patents in suit?

A. The general subject matter is the production and measurement of a low molecular weight form of copolymer-1.

Q. What is the low molecular weight form of copolymer-1 intended for?

A. That's intended for treatment of patients with multiple sclerosis.

Q. You said it was a low molecular weight of copolymer-1. What does the patent technique teach for measuring molecular weight of copolymer-1?

A. The patent teaches the use of size exclusion chromatography.

Q. Mr. Int-Hout, if we could put the cover of the '808 patent

on the screen. Let's look at the title. The title of all of the patents in suit, Dr. Grant is copolymer-1 improvements in compositions of copolymers. Could you tell us what a copolymer is?

A. Yes, but let me start with what a polymer is and then I'll go to what a copolymer is. I prepared a slide.

MR. JAMES: John, if you could put the first slide up, please.

Q. Dr. Grant, using this slide could you explain what a polymer is?

A. Yes. First of all, this slide shows a series of circles or spheres, if you will, that are hooked together by these gray bars and each of these spheres represents what we call a monomer. Mono means one, of course. A polymer is simply many of these single monomers hooked together as depicted here. Poly, of course, means many.

Q. And in a polymer are all of the monomers the same?

A. Yes, they are.

Q. Could you contrast that with what a copolymer is?

A. Yes, on the bottom of the slide I have depicted a copolymer. You see it's very similar to a polymer that it has these monomers hooked together by these gray bars, but in this case colors of all these monomers are different and that just signifies that each monomer of a different color is a different substance and that's what a copolymer is. It's made up of

different monomers.

Q. What are the monomers that make up copolymer-1?

A. They're amino acids.

Q. Can you explain what an amino acid is?

A. Yes, sure. I have a slide. So this slide shows the basic chemical structure of an amino acid. If you look on the left-hand side of the blue box you'll see the N and the two H's. That stands for nitrogen, two hydrogen. Two atoms. That's called an amino group. Then if you look at the right side the red box you see the C, two O's and H, that's carbon, two oxygens and a hydrogen. That's called a carboxylic acid group or acid for short. So you put those two together, you get the amino and acid and the lines that connect these two together are called bonds.

Q. At the bottom of that amino acid there is an R. What is that?

A. That R represents another chemical structure that is different in each amino acid and serves to distinguish one amino acid from another.

Q. Let's move to the next slide.

A. So I guess the best way to show that is to look at the four amino acids that are in copolymer-1. The names are at the top there; glutamic acid, lysine, alanine and tyrosine. In the black structure that's the basic structure of the amino acid is that I described in the previous slide and the colored letters

there such as CH^2 CH^2, carbons, hydrogens the O's are oxygen, those are different R groups. For each amino acid they have a different configuration or different structure.

Q. Dr. Grant, how are those amino acids hooked together in copolymer-1?

A. They're hooked together by peptide bonds.

Q. And what do you call a polymer that's hooked together with peptide bonds?

A. You call them polypeptide because there are many peptide bonds.

Q. Let's go to the next slide. Could you explain what's shown on this slide?

MR. JAMES: Your Honor, with your permission I'm going to approach and hand him a laser pointer.

THE COURT: Sure.

A. So what this slide shows is a short section of a polypeptide. If you notice that, let's just look at the lower left hand part right here, this is the basic structure of an amino acid. We have four amino acids hooked together, they're hooked together by a peptide bond which is highlighted in yellow right here. We have many amino acids in this strain and we have many peptide bonds and that's what's constitutes a polypeptide.

Q. There's a lot of talk in this case about molecular weight. Could you use this slide just to describe the concept of

molecular weight for this molecule?
A. Sure. So the molecular weight of an amino acid or any molecule is simply the sum of the atomic weights of the atoms that it's composed of, so in this particular case if we look at the bottom left hand -- excuse me, right there, the bottom left hand amino acid, you'll see there are some carbon atoms, nitrogen atoms, some hydrogens and some oxygens. If you add up the atomic weight of all those atoms you get the molecular weight of all those acids. In turn, if you add up the molecular weights of all the amino acids you you'll get the molecular weights of the polypeptides.
Q. Where do you find the molecular weight of those atoms?
A. They're found in the periodic table of the elements.
Q. In copolymer-1 are all of the polypeptides the same length and sequence?
A. No, they're not. They're different lengths and different sequences.
Q. Let's look at the next slide. Could you explain what's shown in this slide?
A. This is just an illustration to illustrate the point that you just asked me about, and this just shows the various number of different polypeptides and I'm just depicting them like this by the stream of circles or stream of beads, if you will, and it shows that each one of them has a different length but in addition to that each one of them has a different sequence of

amino acids, which are shown by different letters which stand for glutamic acid, alanine, lysine and tyrosine.

Q. How would you refer to one of those polypeptides; what would you call that?

A. One of those polypeptides would be -- I'm not sure if I understand.

Q. I was just wondering if you could just refer to those as the individual polypeptides or species, if you would?

A. Excuse me. The individual polypeptides are often called species because they all have a distinct molecular weight.

Q. Dr. Grant, could you explain why the polypeptides in copolymer-1 vary in their length and sequence?

A. That's a consequence of the way that copolymer-1 is made.

Q. Did you create any slides and animations to help illustrate this point?

A. Yes, I did.

MR. JAMES: Your Honor, with your permission I'd like to ask Dr. Grant to come down to the screen and explain. If you could stand on the left side.

A. Okay, so we're starting out here with the mixture of these different amino acids; the glutamine acid, lysine, tyrosine, alanine. In this mixture there's a lot more than is shown on the slide, of course, basically thousands or millions of different amino acids and they're all in a vessel of some sort which would be like a flask or something like that and you'll

notice they all have this little loop on them right there. I kind of think it looks like a headphone, but what that loop signifies is that in their present form these amino acids are not able to join to each other yet.

And then we also have this other thing in here this yellow box with an I in it. That's called an initiator and that's another chemical, it's not an amino acid, but it's a chemical that can come in and join with one of these amino acids and when that happens, the polymerization or the growing polypeptide chain process begins. And I have an animation now that we can start to kind of demonstrate how that works.

Q. Before we do that, I had one question. The little loop you said looks like headphones, what is the chemical name for that?

A. That's an N carboxy dihydrate.

Q. So in copolymer-1 the polypeptides are made by polymerizing N carboxy dihydrate?

A. That's correct.

Q. Let's look at the animation.

A. Starting the animation, watch the initiator. It runs into an amino acid, stops right there. You see it hooked into the amino acid made the headphone disappear which means it's now capable of hooking to another amino acid which we've seen happen and its headphone also disappeared. So these are becoming what we call activated, which means they can join to other amino acids. If we keep the animation going, we see the

growing polypeptide chain occurring right here and eventually another initiator up here will come in and a new chain will start.

This process just keeps going on until another initiator comes in gets another amino acid and chains start growing and growing and growing until the reaction is finished and we end up with a mixture of a very, very large number of different polypeptides. And this mixture is non uniform with respect to the lengths of all polypeptides and with respect to all of the amino acid sequences in the polypeptides.

Q. Thank you, Dr. Grant. Now, are the chains that are shown in this slide the actual sizes of the chains in copolymer-1?

A. No they're not. This is just for illustration purposes. The chains themselves are much larger and also they're not, the chains don't have this straight rigid configuration that we've shown here either. That again is just for illustration.

Q. Thank you, Dr. Grant. You can return to the stand, please.

Dr. Grant, if you could turn to Plaintiff's Trial Exhibit 1 again in your binder, and Mr. Int-Hout if you could bring up column 3, lines four through eight. Dr. Grant, on the screen we have column 3 of the patents in suit. Could you read the sentence that's highlighted there beginning at line 6?

A. It says, "The molecular distribution of the two batches was determined on a calibrated gel filtration column." Then it has Superose 12 in parenthesis.

Q. Dr. Grant what is gel filtration?
A. Gel filtration is just another word for size exclusion chromatography. They both mean the same thing.
Q. And what is a gel filtration column?
A. Well, a column is just the vessel in which the gel filtration or the size exclusion chromatography takes place. And I'll have a slide later on kind of showing what column it is.
Q. Dr. Grant, it says that the molecular distribution of the two batches was determined. What is the molecular distribution?
A. Molecular distribution is just a description of the molecular weights of the material that is in the mixture.
Q. When the patents were filed for, were there any other ways to measure the molecular weight distribution of copolymer-1 other than size exclusion chromatography?
A. No, I don't think so. In fact, I mean, I think size exclusion chromatography was and still is the only and best way of determining the molecular weight distribution of a mixture of polypeptides.
Q. So let's look at the next slide. Dr. Grant, is this a slide that you created?
A. Yes, it is.
Q. Could you use this to describe size exclusion chromatography?

A. Yes. This slide then depicts that column we talked about just previously. And all this column is really is just a cylinder. It can be glass or it can be metal, but it's the vessel in which the chromatography itself takes place.

Q. Put up the next slide. Dr. Grant, this slide shows some little brown circles inside that column. What are those?

A. Those brown circles are called the separation gel. They are the actual solid or matrix, as we call it, that the separation of the polypeptides takes place on and in addition to that, we show that there's liquid there too. These beads are placed into the column in liquid.

Q. Dr. Grant, did you bring anything for show and tell today so you could show what those beads look like inside the column?

A. Yes, I did. Oh, there it is. Thank you. I brought a sponge. The beads in the slide look like they're solid, but in fact they're not. They're more like this sponge that has a lot of channels or pores in it, and what that does is if you have a large molecule, let's say, for instance, like the fist of my hand it's too large to get into the sponge because it's much larger than these pores, but if you have a small molecule like the tip of my finger it can penetrate into these pores. That's how size exclusion chromatography works.

The molecules you're trying to separate can either get into the pores or they can't and that process gives you the separation. And I'll demonstrate in a minute how that happens.

Q. Thank you. Now, how is the sample introduced into the column?
A. It's just introduced into the top of the column by some method. You can use an injector or in this case we show it's just a pipette, which is basically like straw.
Q. What happens to them after they're introduced?
A. After the sample is introduced, you start the liquid flowing into the column and that brings the sample down through the column and as it goes through the column the large molecules separate from the small molecules as depicted here. You see the larger kind of purple-ish molecules are at the bottom, the very small red or brown molecules are at the top yet.
Q. Let's go to the next slide and the next one. Dr. Grant, we've shown two boxes out to the right on slide 15. Could you explain what those are?
A. Yes, this first box -- I'm laser challenged. This first box is just a blowup of the very small edge of one of these beads. You can see the dark spots. These are the pores starting to appear. Now, if you take and blow up the edge of that you can see these here and these are the pores that are in this gel much more distinctly.
Q. Play the animation, John.
A. So this animation shows the molecules coming down and encountering these pores. I'll run it a couple of times. You

see the large molecules aren't able to get into the pores very well while the small molecules are. Let's go one more time. So the large molecules can't get into these pores, so they pass through very quickly, but the small molecules have to go into these pores and pass some time so they get delayed and as a result they come out much later than the large molecules and that's how size exclusion chromatography works.

Q. Okay, let's go to the next slide, Mr. Int-Hout. Maybe an animation. Yes, Dr. Grant, could you tell us what's shown on -- please stop that. Thank you. What's shown here, Dr. Grant?

A. So again we have a column with our gel matrix or beads inside and blind sample to the top and separation will take place. But now we have a tube that's connected to the bottom of the column and this tube is going over to an instrument that we call a detector and what this detector does, it senses the presence of these molecules and also the quantity or the weight of the molecule that's coming out of the column.

Q. All right, so let's let the animation run. Could you describe what's happening here?

A. So we see the separation process happening again. I'm having trouble with this pointer, I'm sorry. There it is. Molecules are coming out, they're passing this detector and the detector is sensing their presence.

Q. Now, let's go a little further. Stop right there. Doctor,

in this particular slide you've shown an XY coordinate in the upper left-hand corner. Could you explain what that is?

A. Yes. This is how we're going to record what the detector sees. So as the molecules pass -- let me talk about what the axis are first. The Y axis shown first is simply the amount of the material that's passing the detector and the X axis is labeled time and time goes from the left to the right so molecules are coming out of the column at different times because the big ones are not being delayed and the small ones are being delayed so as they pass the detector we'll record that on this graph here.

Q. Let's let that run.

A. This animation will show how that happens in an illustrated way. So as the molecules come out and they pass the detector here, you see that their presence is being sensed and the amount is being recorded and it gets up to a peak and then it starts going back down and at the end. When all the molecules are passed through we're back down to baseline.

Q. Dr. Grant, I notice that the big molecules came out first but the line only deflected a little bit where you have 25 minutes or so. Why is that?

A. That's because at this point in time the detector is not measuring the molecular weight of the molecule, it's just measuring how much of it is there, so even though the big ones are coming out, there may be at the very beginning only a small

amount of them.
Q. Now, this graph that you're showing in the upper left-hand corner, does it have a name?
A. Yes, it's called a chromatogram.
Q. Now, Dr. Grant, let's put up the next slide. And, John, if you could put in the curve. We were talking about a chromatogram. Could you describe for us or tell us what a chromatogram shows us?
A. Once again we have two axis on the graph, one, the Y axis, the amount of material that's shown by the detector and then on the X axis is the time, the times going from left to right. So those are zero time to however much time it takes to run the chromatogram.
Q. Does the chromatogram depict all of the molecules in the sample?
A. Yes, it does. You start out at the beginning with no molecules being detected. All molecules pass through. At the end there are no molecules being detected. That's 100 percent of the molecules going through that column.
Q. How do you determine the molecular weight of the molecules that are coming out and are shown on the chromatogram at any particular time?
A. Well, remember I said that the big molecules come out first or at an early time, the small molecules at later time so you have to develop a key where you can correlate the time that

they come out of the column with the molecular weight.

Q. What is that key called?

A. The key is called a calibration.

Q. Was this idea of a calibration understood in 1994?

A. Yes, it was.

Q. I'd like to talk a little bit about how that calibration process is carried out. How do you create a calibration, Dr. Grant?

A. I'm going to illustrate that on the next slide. And what this slide shows labeled standards is another chromatogram. Again, we have the amount on the Y axis and the time is along the X axis going from left to right.

What this chromatogram shows is it shows five different substances that come out of this column and this substance right here comes out early and this substance on the right has come out late and these are called standards, and they're called standards because we've already determined what their molecular weight is. Okay? So if we know what their molecular weight is and you know what time they've come out of the column, we can plot that. And I show that at the bottom of the slide.

Now I'm plotting the molecular weight versus time and I just correlate the time that the molecules, the standards come out of the column and bring that down to the axis on the time and since I know the molecular weight I can go up on the Y

axis to find that molecular weight and come over and produce a point. If I then do that for all of the standards, I produce a series of points and when I have all the points, I draw a line through there and this line is the calibration or the key that you use to determine molecular weight of your sample.

Q. Dr. Grant, how do you know the molecular weight of those standards?

A. You determine it by some other method besides size exclusion chromatography and there are several different methods that can be used.

Q. Dr. Grant, after you get your calibration, what do you do with it?

A. Once you get your calibration then you compare it to the chromatogram of your sample which I'm now showing again at the top of this slide. Again, just to reiterate, this chromatogram shows the amount of material and the time that these material comes out of the column, so if you want to find the molecular weights let's say of the peak up here, you find out what time it came out of the column, you correlate that to the time that's on your calibration curve down here -- I keep losing this, I apologize. Correlate it to the time of your calibration curve and then go over to the Y axis and you can read your molecular weight off directly. You can do that for any other point on the chromatogram. You can do it for a time early, time late, any time on that chromatogram and determine

what the molecular weight that has come out of that column is at any point in time.

Q. We come back to standards, what characteristics do you look for when choosing standards?

A. When you're doing what I call conventional chromatography, which is what I've been describing here, you look for standards that have the same size to molecular weight relationship as your sample does.

Q. Let's put up the next slide. Perhaps you can use this to explain that concept, Dr. Grant.

A. Okay, yes. This slide shows two polypeptides, shall we say, one on the left here, that's basically just a string and that string is relatively short. The one on the right is also a string, but you see that string is much, much larger. Now, both of these polypeptides have basically the same kind of confirmation that we call loosely coiled, you can see they're very loosely wound and what this means is that the large one on the right having much bigger size will come out of the column earlier than the smaller one on the left, even though they're the same type of confirmation or coil, if you will.

Q. Dr. Grant, those molecules shown on the screen, they look flat. Are they flat?

A. No, they're actually three dimensional. If you can draw a circle around them, kind of show their circumference and then imagine that's not a circle but a sphere. It's in three

dimensions and you can turn it around, see it has three dimensions and that's what a molecule basically looks like in solution.

Q. That volume that the molecules have in solution, what is that called?

A. That's called a hydrodynamic volume.

Q. Was the concept of hydrodynamic volume well known in 1994?

A. Yes, it was.

Q. So Dr. Grant, let's look at the next slide and here we show something called a tightly coiled standard in the center. Can you explain what's shown on here?

A. Yes. In the center of this tightly coiled standard, although you can't really see, is a very, very long string, but it's all tightly coiled, wrapped up very tightly, but you see by drawing your circle around here and imaging it as a sphere they both have the same size, even though they don't have the same length or the same molecular weight, if you will. And what this means is that even though they have the different molecular weight, if they have -- there we go, even though they have a different molecular weight, they have the same size, so they're going to come out of the column at the same time.

Q. And, Dr. Grant, if we look at the right side of the slide now and can you contrast that with the red standard in the middle and the larger peptide or the larger molecule on the right?

A. Yes. So the red molecule in the middle has a string, if you will, that's the same length as the green molecule on the right, but it has a different size, so even though they're the same molecular weight, they'll come out of the column at a different point. That's opposed to the fact that the green molecule on the left is a much shorter length of fragment of string, but it's the same size, so even though it isn't the same molecular weight, it will exit the column at the same time. And what this underscores is the fact that you have to have the same size molecular weight relationship or volume to molecular weight relationship with your standards as you do for your sample in order for the size exclusion chromatography to work.

Now, I've been explaining conventional size exclusion chromatography. There's another type of calibration that you can do called universal calibration that doesn't require this relationship, but it uses a different physical property called viscometry that adjusts for it and gives you accurate molecular weights also. There's two types of calibration that can be used.

Q. With respect to what you called conventional calibration, was the concept of matching the standards in the sample known to scientists in 1994?

A. Oh, yes, it was. I mean, in fact, when I was learning how to do size exclusion chromatography in the 1970's, it was one

of the very, very first things that I was taught.

Q. Now, Dr. Grant, do you have an understanding as to how many patents are being asserted by the plaintiffs against the defendants in this litigation?

A. Yes. There are nine.

Q. And have you examined the claims that are being asserted by the plaintiffs against the defendants?

A. I have.

Q. Have you prepared any slides categorizing the asserted claims of the patents in suit?

A. Yes, I have.

Q. Let's put up the next slide. Dr. Grant, can you explain how you categorize the claims?

A. I grouped them into three categories. The first is the average molecular weight and then the copolymer-1 molar fraction and then finally the TFA copolymer-1 molar fraction.

Q. We'll come back to average molecular weight in just a moment. Dr. Grant, can you explain what copolymer-1 molar fraction means?

A. Yes. Copolymer-1 molar fraction simply means that you can determine the number of molecules of any component in a mixture and determine whether or not their molecular weights are between certain bounds of molecular weight.

Q. And those are copolymer-1 molecules?

A. Yes, they are.

Q. What is the last bullet TFA copolymer-1 molar fraction? What does that refer to?

A. TFA copolymer-1 molar fraction refers to TFA copolymer-1, which is an intermediate on the way to making copolymer-1.

Q. What does TFA stand for?

A. That stands for trifluoroacetic.

Q. And is trifluoroacetic copolymer-1 used in the processes that are proposed by the defendants?

A. Yes, it is.

Q. Now, Dr. Grant, I'd like to go and focus on the average molecular weight claim limitations. Have you created a slide that categorizes the average molecular weight limitations that you have analyzed?

A. Yes, I have.

Q. Let's look at the next slide. Dr. Grant, can you explain what's shown on this slide, please?

A. Yes. This slide shows the three limitations that we're going to be talking about today, as far as average molecular weight is concerned. They are at the top about 5 to 9 kilodaltons, and they're found in claim 1 of the '808 patent, that is found in claim 1 of the '808 patent and claim 1 in the '589 patent.

The next one is about 4 to about 9 kilodaltons. That's found in claims 1 and 6 of the '847 patent, and also claims 1, 8, 9, 12, 23, 30 and 31 of the '539 patent.

And the last category, the last claim is 6.25 to 8.4 kilodaltons, and that's found in claim 10 of the '539 patent.

(Continued next page)

BY MR. JAMES:

Q. Thank you. Dr. Grant, and you understand that the Court has construed the term average molecular weight, correct?

A. Yes, I do.

Q. Let's put up the Court's claim construction? Could you read that into the record, please?

A. Yes. It says that: The peak molecular weight detected using an appropriately calibrated suitable gel filtration column.

Q. Is this the definition of average molecular weight that you have used in rendering your opinions in this case?

A. Yes, it is.

Q. You understand that Sandoz and Momenta have filed an application with the FDA to sell generic form of Copaxone?

A. Yes, I do.

Q. And have you examined the documents that were submitted by Sandoz and Momenta to the FDA regarding that proposed product?

A. Yes, I have.

Q. Now based on your review, have you formed an opinion as to whether the generic Copaxone product proposed by Sandoz and Momenta meets the average molecular weight limitations of the asserted claims?

A. Yes, I have. And in my opinion both products produced by Sandoz and Momenta meet all of the molecular claims in the patents.

Q. Let's look at plaintiff's trial Exhibit 209 in your binder, Dr. Grant.

A. 209-R, okay.

Q. Yes, I believe in your binder you have the redacted form of 209. Do you recognize that document, Dr. Grant?

A. Well, it's got a blank page, but I see on the top it says elucidation of structure and characteristics. I think that is this, the ANDA, Sandoz's ANDA from the December of 2007.

Q. Okay. And could you look at the date in the upper right-hand corner? What's the date?

A. December 26, 2007.

Q. Now, did you rely on this section, of the defendant's ANDA of Sandoz, Momenta ANDA in rendering your opinions in this case?

A. Yes, I did.

MR. JAMES: And, your Honor, we like to offer into evidence plaintiff's trial Exhibit 209, the unredacted version of 209.

MR. ACKER: We object to. We wish for the unredacted version, but just for the Court's purposes. Redacted version should not be permitted into evidence.

THE COURT: Only the redacted version will be made

public.

MR. ACKER: Very well. That's fine. No objection, your Honor.

THE COURT: Okay. It's admitted.

(Plaintiff's Exhibit 209 received in evidence)

MR. JAMES: Thank you, your Honor.

Q. Now, Dr. Grant, let's turn to page 2017 in plaintiff's trial exhibit 209.

A. Okay.

Q. Do you have that?

A. Yes.

Q. Could you tell us what this section of the ANDA describes, Dr. Grant?

A. Yes. This is a section of the ANDA entitled more mass Mp by SEC RI using peptide standards.

Q. Perhaps you could unpack that title a little bit for us; what does that mean?

A. Yeah. Well, the abbreviation Mp refers to peak average molecular weight. And then SEC, of course, is size exclusion chromatography. And RI stands for the type of detector that was used in this instance, it's a refractive index detector, excuse me. And then it says it is used peptide standards and these are synthetic poly peptides that have been produced for this purpose.

Q. And what have the peptide standards been used for?

A. They've been used to calibrate the column that's used to determine the molecular weight of the substance.

Q. Mr. Aannestad, if you could pull up the introductory paragraph there. Dr. Grant, could you read the first sentence into the record, please?

A. Yes. The Copaxone package insert lists the average molecular weight of glatiramer acetate as 5,000 to 9,000 daltons.

Q. Did Sandoz and Momenta, did they set the average molecular weight 5,000 to 9,000 kilodaltons -- I'm sorry -- let me ask that again. Did Sandoz and Momenta set average molecular weight 5,000 to 9,000 daltons as a specification for their product?

A. Yes, they did.

Q. And, in your opinion, do Sandoz's and Momenta's ANDA batches meet that 5,000 to 9,000 dalton specification?

A. Yes, in my opinion both Sandoz and Momenta's batches meet that specification.

Q. Looking at the next paragraph down under analytical method, does this section of the ANDA indicate how Sandoz and Momenta measured the molecular weight of their product.

A. Yes. It says that they used size exclusion chromatography.

Q. Does it say what kind of columns they used?

A. Yes. They're listing TSK gel G 3,000 and G. 2,000 columns.

Q. What are those?

A. Well, those designations are just the manufacturer's names for these columns. But what they are are size exclusion chromatography columns that have been developed for the purpose of, among other things, separating polypeptides based on their molecular weight.

Q. And could you read the next sentence in that begins with nine peptide reference standards, could you read that into the record please, Dr. Grant?

A. Nine peptide reference standards with amino acid compositions consistent with glatiramer acetate covering the molecular weight range from 1,500 daltons to 12,000 daltons are used to calibrate the retention time axis in order to determine an accurate measurement of Mp.

Q. Now, do you have an opinion as to whether the peak molecular weight values determined by Sandoz and Momenta were detected using an appropriately calibrated suitable gel filtration column?

A. Yes, I do. I believe that the columns that they list here are suitable for that purpose, in fact developed for that purpose, and that the standards that they're using are standards that would give you an appropriate calibration of this column.

Q. And why do you believe those standards would give you appropriate calibration?

A. Well, there were synthesized specifically to be like

co-polymer-1. They have the same four amino acids. They have the same -- they have, in this case a nearly random sequence of amino acids, and they will, in my opinion they'll have the characteristics that standards would have to have in order to accurately measure the molecular weight of the polymer-1?

Q. What characteristics would those be?

A. Same size to molecular weight relationship as co-polymer-1.

Q. And, Dr. Grant, could you turn to plaintiff's trial exhibit 349 in your binder?

A. Okay.

Q. I realize that is an redacted version of the exhibit. With that in mind, Dr. Grant, could you flip through it and tell me whether you can identify this document?

A. Lot of blank pages.

Q. Yes.

A. I think based upon the title of the document, elucidation of structure and other characteristics and some of the things that I see that are not redacted, that I have seen this.

Q. Perhaps you can look at page 17948.

A. Okay.

Q. Do you have that?

A. I do.

Q. You recognize that?

A. Yes, I do.

Q. Does this refresh your recollection that you relied on

plaintiff's trial Exhibit 349 in rendering your opinions in this case?

A. Yes. It's the same segment section of the ANDA that we looked at before, and if I recall, it was a later version.

Q. Did you rely -- you relied on this document in rendering your opinions, Dr. Grant?

A. Yes, I did.

MR. JAMES: Your Honor, we would offer into evidence plaintiff's trial Exhibit 349, in its unredacted form.

THE COURT: With the same understanding.

MR. ACKER: Yes, your Honor, that's fine.

THE COURT: All right, thank you. It's admitted.

(Plaintiff's Exhibit 349 received in evidence)

Q. Dr. Grant, looking at page 17948, in this later submission did Sandoz and Momenta change their protocol from measuring molecular weight from the way that they had reported it previously?

A. No, they did not.

Q. If you look at the page 17948 that you have open there, could you tell the Court what's found on that page?

A. Well, again, it's a section of the ANDA that's entitled more mass Mp by SEC RI using peptide standards.

Q. And I'd like you to look at one particular portion of the in -- the analytical method section, in that paragraph the -- could you pull that paragraph up.

A sentence we read a few minutes ago Dr. Grant, about the nine peptide reference standards and it says that they're used to calibrate the retention time axis in order to determine an accurate measurement of Mp; you see that?

A. I do.

Q. What does that mean to you, Dr. Grant?

A. Well, it means that they believe that these peptide standards that they were using had the same size molecular relationship as the substance they were measuring and that it would give you a very accurate measurement of what that molecular weight would be.

Q. What do you understand accurate to mean in this context?

A. I understand accurate to mean the fact that it will represent the actual, the real molecular weight of the product.

Q. Do you understand Sandoz's product to be non-uniform with respect to molecular weight in sequence?

A. Yes, I do.

Q. And if you look at page 17949, the next page, Dr. Grant, are there specific molecular weight values provided on that page?

A. There are.

Q. Turn to that page. And I'd like to focus first on table 21, Dr. Grant. What information is provided in table 21?

A. Okay, table 21 lists six lots of Sandoz's glatiramer acetate drug substance. It shows the name glatiramer acetate

on the left, in the middle shows the lot number, and on the right it shows the results of the analysis and lists the peak molecular weights in daltons.

Q. Dr. Grant, you mention this was a drug substance. What is the drug substance?

A. The drug substance is the active ingredients in their product.

Q. And can you, for the record, can you read in the peak molecular weights for those six lots of drug substance, please?

A. Yes. Starting from the top, we have lot 077K7277. It presents a mean or average molecular weight of 8,407. And that's from two determinations, that's N equal two means.

Then lot 087K7253 presents a mean peak average molecular weight of 7,275, again from two determinations.

Lot number 029K7279 has a mean of 7,641 from two determinations.

Lot number 049K7275 has a single molecular weight listed of 6,977.

Lot number 049K7276 has a molecular weight of 7,366.

And lot number 059K7275 has a molecular weight of 7,199.

Q. Thank you, Dr. Grant. I'd like to look now down, further down the page to table 22. Dr Grant, what information is provided in that I believe 22, of plaintiff's Exhibit 349?

A. This is a similar table. Now it lists two lots of

glatiramer acetate injection, which is Sandoz's drug product and also the peak average molecular weights that were determined for them.

Q. And what are those peak molecular weights?

A. For lot CT0743, it lists a mean molecular weight of 8,274 from two determinations.

And for lot CT0750, it lists a mean of 7,417 from two determinations.

Q. All right, thank you. Now, Dr. Grant, when it refers to glatiramer acetate there, do you have an understanding what that is or glatiramer acetate is; did Sandoz tell the FDA what?

A. They said it was co-polymer-1.

Q. Let's look in your binder at plaintiff's trial Exhibit 206.

A. Okay.

Q. Dr. Grant, can you identify that document?

A. Yes. This is again a portion of ANDA that deals with a draft of their package insert.

Q. And is this a document that you reviewed in rendering your opinions in this case?

A. Yes, it is.

Q. Dr. Grant, I'd like to look under description. Could you read in the first part of the first sentence under description?

A. Yes. It says, "glatiramer acetate, in parentheses, formerly known as co-polymer-1.

Q. What does that convey to you, Dr. Grant?

A. That conveys to me, excuse me, conveys to me that Sandoz thinks that their product, glatiramer acetate, is co-polymer-1.

MR. JAMES: And, your Honor, we would offer into evidence plaintiff's trial exhibit 206?

MR. ACKER: No objection, your Honor.

THE COURT: Admitted.

(Plaintiff's Exhibit 206 received in evidence)

Q. Dr. Grant, could you turn in your binder to plaintiff's trial Exhibit 351, please. I recognize what you had in your binder is redacted, but, Dr. Grant, can you look at that and tell me if you recognize plaintiff's Exhibit 351?

A. Yeah. From the top part of the first page it's another portion of the ANDA that deals with batch analysis.

Q. Did you rely on plaintiff's trial Exhibit 351 in rendering your opinions in this case?

A. Yes, I did.

MR. JAMES: Your Honor, we would offer into evidence plaintiff's trial Exhibit 351?

MR. ACKER: No objection, your Honor.

THE COURT: All right, admitted.

(Plaintiff's Exhibit 351 received in evidence)

Q. Dr. Grant, if you look at tables two and three of plaintiff's trial Exhibit 351, what information is provided in those tables? That's on pages, for the record, 18608 through 18611.

A. Okay. The Copaxone that I have shows a portion of a table. The rest of it has been redacted. That's labeled batch analysis for glatiramer acetate, and it lists several lots, and it -- two rows that are left in my binder are rows that deal with molar mass and amino acid composition.

Q. Okay, let's look at, in table two, the row labeled TP-116. Do you have an understanding what TP116 is, Dr. Grant?

A. It's the test method that they used to determine the molecular weight of their product.

Q. And under acceptance criteria, could you read into the record what that says?

A. Yes. It says Mp is greater than or equal to 5,000 daltons, and is less than or equal to 9,000 daltons.

Q. What does that convey to you, Dr. Grant?

A. Well, that conveys to me that they expect their product to be -- to have an average molecular weight, a peak average molecular weight between 5,000 and 9,000 daltons.

Q. Dr. Grant, what range of values are provided for the peak average molecular weights in table two of plaintiff's trial Exhibit 351?

A. The table lists five different lots, and the range of molecular weight values that are there are from 5,932 daltons, to 8,407 daltons.

Q. And if we look at table three, Dr. Grant, what information is provided under the row TP-116?

A. TP-116 once again provides peak average molecular weight determinations for one, two, three, four lots.

Q. And what are -- what's the range of values that's provided there?

A. The range of values here is 6,977 to 7,641.

Q. All right. Now, Dr. Grant, have you prepared a slide summarizing the peak molecular weight values that are reported in the ANDA for the various lots of Sandoz's glatiramer acetate?

A. Yes, I have.

Q. Let's look at the next slide, John. Dr. Grant, what is shown on this slide, slide 26?

A. Okay, this slide shows the peak average molecular weight values that we've just been talking about for the various lots. On the left-hand side the lot numbers are presented there, and then on the right-hand side the peak average molecular weights in daltons are listed.

Q. And, Dr. Grant, is this a slide that you created?

A. It is.

Q. Now, have you made a determination as to which average molecular weight claim limitations are met by these lots?

A. Yes, I have.

Q. Let's look at the next slide. Now, Dr. Grant, which of these lots satisfy the molecular weight claim limitation of about five to about nine kilodaltons?

A. In my opinion, all of these lots satisfy that claim limitation.

Q. And for the record I've read that incorrectly. It's about five to nine kilodaltons; is that correct?

A. Yes.

Q. And let's look at the next part of this, Dr. Grant. Which of these lots meet the limitation of average molecular weight about four to about nine kilodaltons?

A. In my opinion, all of these lots meet that claim limitations.

Q. And looking at the last average molecular weight limitation, 6.25 to 8.4 kilodaltons. Dr. Grant, which of the lots meet that limitation?

A. In my opinion, all but one of the lots meet that claim limitation.

Q. And why did you leave that one lot out of your analysis?

A. I left that out -- didn't put a check mark there because the value of 5,932 does literally fall between 6.25 and 8.4 kilodaltons.

Q. Dr. Grant, do you have an opinion as to whether if Sandoz and Momenta used the process in their ANDA to make co-polymer-1 product, whether their product would fall within the average molecular weight claim limitations of the asserted -- in the asserted patents?

A. Yes. In my opinion, if Sandoz and Momenta uses the process

that's described in their ANDA, all of their products will meet all of these claim limitations.

Q. Dr. Grant, I'd like to look at the -- go back to the grouping of molecular weight limitations that we looked at earlier, come back to co-polymer-1 molar fraction. Could you explain again what co-polymer-1 molar fraction refers to?

A. Yes. Well, of course it refers to co-polymer-1, and molar fraction simply refers to determination of the number of molecules in this case that have a distinct molecular weight, species molecular weight, if you will, between an upper and lower bound of molecular weight.

Q. And could you turn in your binder to plaintiff's trial exhibit nine, that's a copy of the '098 patent. And if you could bring up claim one.

Dr. Grant, with respect to molecular weight, perhaps we could start with you reading into the record the highlighted portion of claim one of the '098 patent?

A. Okay. It says, over 75 percent of the copolymers in the mixture, on a molar fraction basis, have a molecular weight in the range of two kilodaltons to 20 kilodaltons, and less than 5 percent of the copolymers have a molecular weight above 40 kilodaltons.

Q. Okay. And what does it mean there that they, the copolymers in the mixture on a molar fraction basis have a molecular weight in that range?

A. Molar fraction again, referring to individual molecules. And if you remember, if you think about co-polymer-1 is a mixture, that mixture is composed of individual molecules. And each of these molecules have their own distinct molecular weight.

So what this is saying is that for co-polymer-1, the molecular weights of 75 percent of those molecules are between two and 20 kilodaltons, and the molecular weights of 5 percent of those molecules are above 40 kilodaltons.

Q. Now, Dr. Grant, did you create a slide showing which claims contain the co-polymer-1 molar fraction limitations?

A. Yes, I did.

Q. Let's go to the next slide. Dr. Grant, could you explain what's shown in slide 29, please?

A. Yes. It shows the four co-polymer-1 molar fraction limitation. The first one is over 75 percent, between two and 20 kilodaltons. And that is claims one to three of the '430 patent.

The second is less than 2.5 percent above 40 kilodaltons. And that's claims 8 and 30 of the 539 patent.

The next also is over 75 percent between two and 20 kilodaltons, and less than 2.5 percent over 40 kilodaltons, and that's found in claims 9, 10 and 31 of the '539 patent, and also claim 8 of the '098 patent. And then the last is over 75 percent between two and 20 kilodaltons and less than

5 percent over 40 kilodaltons, and that is found in claim one of the '476 patent, claim one of the '161 patent, and claim one of the '098 patent.

Q. Thank you, Dr. Grant. Have you created a slide in order to try to illustrate for the Court what this molar fraction limitation actually means?

A. Yes, I have.

Q. Let's look at the next slide.

A. So once again we have a chromatogram. And just to remind you that this chromatogram, the big molecules come out early, the smaller molecules come out later. So I've depicted 40 kilodaltons as coming out first, then 20 and then two.

Chromatogram represents the amount of material that is found at any particular time which is along the X. axis going from left to right. And as I said before, this chromatogram is composed of a very very large number of individual molecules. Each these molecules has a distinct molecular weight. And what size inclusion chromatography allows you to do is to perform the separation and determine how many of those molecules have molecular weight between any particular bounds, in this case I listed 40, 20 and two because those are the molecular weight within the claim limitations.

Q. All right, thank you. Now, can you just take the area under the curve under the chromatogram and determine the molar fraction that, the percentage on molar fraction basis, Dr.

Grant?

A. No, you can't do it that way.

Q. Why is that?

A. It's because the curve as shown here is basically linear scale and the relationship between time and molecular weight is a log scale. So by merely taking the area under that curve is going to distort the results.

Q. Dr. Grant, did you create a slide in order to illustrate how you calculated the molar fractions?

A. Yes, I did.

Q. Let's go to the next slide. What is shown on slide 31?

A. Well, so what I've done with this slide to illustrate this is to just show that the chromatogram is divided into a bunch of different segments or slices, as we call them. And these are just small rectangles. And each one of these rectangles, the area within the rectangle represents a certain amount of material. And then what you need to do is you need with your calibration curve to assign molecular weight to each of these slices. And then when you assign molecular weight to each of the slices, you can divide the amount of material by the molecular weight to give you the moles of material in each slice.

Q. What are moles?

A. Moles are just a measure of the number of molecules that are present.

Q. So I just want to make sure I understand. Each little rectangle represents an amount of material --

A. Yes.

Q. -- coming out?

A. That's correct.

Q. And then you assign it a molecular weight?

A. That's correct.

Q. And then what do you do with those two values?

A. Well, as I said, once you assign the molecular weight, you can divide the amount by the molecular weight to give you moles.

Then between any two bounds, for instance, the two kilodaltons and the 20 kilodaltons that you have here, you can add up all of those moles. And if you then compare that to the total number of moles of the whole chromatogram, you will get a percentage value for the fraction of the number of molecules that are between these two molecular weight bounds.

Q. Dr. Grant, did you create a slide to show the mathematical calculation that you used to calculate the percentage?

A. Yes, I did.

Q. Let's look at the next slide?

A. So this just shows the math, it's very simple. On the top it's shown that you determine the number of molecules between two kilodaltons and 20 kilodaltons, and divide that by the total number of molecules in the entire chromatogram, and just

multiply by 100 percent. You get the percent of molar fraction between two and 20 kilodaltons. Then a very similar manner on the bottom I show that if you determine the number of molecules greater than 40 kilodaltons, and divide that with a total number of molecules in the chromatogram, multiply by 100 percent, you get the percent mole fraction above 40 kilodaltons.

Q. Okay, thank you. Now, on the slide you have a number of molecules but a minute ago you said that you do some division and get the number of moles. What's the relationship between those two things?

A. Number of molecules and moles are basically the same thing.

Q. Now, did Sandoz and Momenta, did they provide you with the data necessary to determine whether the molar fraction claim limitations were satisfied by their product?

A. Yes, they did.

Q. In what form were those data provided to you?

A. They were provided to me on a secure flash drive in a software package called in power.

Q. And using those data, did you analyze whether the product, the Sandoz proposed drug substance meets the molar fraction claim limitations?

A. Yes, I did.

Q. Now, in order do that, Dr. Grant, did you have to extract individual polypeptides from the samples and measure their PL

molecular weights in order to determine the molar fractions?
A. No, of course not. As I said before, you can't do that. But what size exclusion chromatography does for you is it gives you the ability to do basically the same thing. It separates the molecules based upon their individual sizes and allows you to calculate the number of molecules that are between any molecular weight bounds.
Q. Size inclusion described in the literature for this purpose, that is determining the percent molar fraction of molecules above or below a particular molecular weight?
A. Yes, it is. It's been used by many many scientists for many many years for this exact purpose. And I said earlier it's probably -- it is the only method that we have that enables us to do this.
Q. Now, the data you were provided, was that a large amount of data?
A. Yes, it was. When we extracted it from the empower software and put it into an Excel spread sheet it was very, a lot of numbers of pages. I don't remember how many, but a lot.
Q. And did you work with anyone to perform the calculations Dr. Grant?
A. Yes. I worked with Dr. Paul Winter at Chemir Analytical Laboratories in St. Louis.
Q. What was Dr. Winter's involvement.
A. Dr. Winter was an expert in empower software, so he

assisted me in extracting the data and putting it into excel spread sheet and then he held me make the calculations.

Q. Did Dr. Winter perform any independent calculations on the data?

A. No. He only did what I instructed him to do.

Q. Now, have you prepared a slide which shows a summary of the results of your calculations, Dr. Grant?

A. Yes, I have.

Q. Let's look at the next slide. Dr. Grant, could you tell us what's provided on slide 33?

A. Yes. It's a summary of the results that I produced from the data that was provided by Sandoz. It deals with five different lots, which are listed over on the left-hand side. Then middle column to the right has the results for the percent lower fraction between 220 kilodaltons percentage, and then the last column on the right has the results for percent lower fraction above 40 kilodaltons.

Q. Dr. Grant, could you read the values for each lots into the records, please?

A. Yes. So for lot 077K7277, the molar fraction between two and 20 kilodaltons was greater than or equal to 91.99 percent and the molar fraction above 40 kilodaltons was less than or equal to 0.36 percent.

For batch lot, excuse me, O87K7253, molar fraction between two and 20 kilodaltons was greater than or equal to

85 percent, and molar fraction above 40 kilodaltons was less than or equal to 0.28 percent.

For lot number 049K7275, molar fraction between two and 20 kilodaltons was greater than or equal to 90.82 percent, and the molar fraction above 40 kilodaltons was less or equal to 0.23 percent.

For lot number 049K7276, molar fraction between two and 20 kilodaltons was greater than or equal to 87.36 percent and percent molar fraction above 40 kilodaltons was equal to or less than, less than or equal to 02.24 percent.

And for the lot 059K7275, the percent molar fraction between two and 20 kilodaltons was greater than or equal to 88.83 percent, and the percent lower fraction above 40 kilodaltons was less than or equal to 0.25 percent.

Q. Thank you, Dr. Grant.

MR. JAMES: While you catch your breath and take a drink of water, your Honor, we would like to offer slide 33 under Rule 1006 as a summary of the calculations that Dr. Grant performed on the date data he was provided.

MR. ACKER: No objection?

THE COURT: Any objection? Admitted.

(Plaintiff's Exhibit 33 received in evidence)

Q. Dr. Grant, do you have an opinion as to whether Sandoz's glatiramer acetate drug product in drug substance satisfied molar fraction claim limitations?

A. Yes, in my opinion their drug substance satisfies all, all of these molar fraction claim limitations, excuse me.
Q. Let's put up the next slide. Dr. Grant, can you tell us -- there we go -- thank you, John -- which of the lots that you analyzed had over 75 percent on molar fraction basis of the copolymers between two kilodaltons and 20 kilodaltons?
A. In my opinion, all of the lots had that molar fraction.
Q. Dr. Grant, which of the lots had less than 2.5 percent on a molar fraction basis of copolymers above 40 kilodaltons?
A. Again, in my opinion all of the lots met that limitation.
Q. And how many of these batches, Dr. Grant, had both over 75 percent of the copolymers between two kilodaltons and 20 kilodaltons and less than 2.5 percent copolymers above 40 kilodaltons?
A. In my opinion, all of them had that limitation also.
Q. And finally for the record, Dr. Grant, which of the batches that you anaylzed had both over 75 percent on a molar fraction base copolymers between two and 20 kilodaltons and less than 5 percent copolymers over 40 kilodaltons?
A. In my opinion, all of the lots met that limitation.
Q. Dr. Grant, if Sandoz and Momenta make co-polymer-1 using the process described in their ANDA do, you have an opinion as to whether the product will meet the co-polymer-1 molar fraction limitations of the asserted claims?
A. Yes. If Sandoz Momenta used the process described in their

ANDA, all of their products will meet these molar fraction limitations.

Q. Let's look now at the last set of the molecular weight limitations, TFA co-polymer-1 molar fraction. And, Dr. Grant, just if you remind us very briefly again what are, what is a TFA co-polymer-1 molar fraction?

A. TFA co-polymer-1 is an intermediate on the way to co-polymer-1. It simply has these trihguoracetyl protecting groups on all of the lysine residues, and once again the molar fractions are the number of molecules of the components and mixture that would fall between any particular molecular weight boundary.

Q. Did you create a slide that shows for the Court illustrates what TFA co-polymer-1 looks like?

A. Yes, I did.

Q. Dr. Grant, what's shown here on slide 38?

A. So this slide just illustrates the short segment of co-polymer-1 made up of the four different amino acids, glutamic acid, lysine alamine and tyrosine. And on the lysines, those are the ones with the Ls, we see those little blacks boxes, and those black boxes represent the trihguoracetyl group.

Q. Does the trihguoracetyl group have a known molecular weight?

A. Yes, it does.

Q. Let's look at claim one of the '430 patent. That's PTX-4, Dr. Grant. And if we could look at claim one, Mr. Aannestad. Dr. Grant, with respect to the trihguoracetyl co-polymer-1 molecular weight limitation, what does claim one of the '430 patent require?
A. It requires that over 75 percent of the molecules in trihguoracetyl co-polymer-1 are within the molecular weight range of about two kilodaltons to about 20 kilodaltons.
Q. And did you create a slide that summarizes which of the claims, the asserted claims of the patents in suit have this trihguoracetyl co-polymer-1 limitation?
A. Yes, I have -- I did.
Q. Let's look at the next slide. Dr. Grant, could you explain for the Court slide 39, please?
A. So this is the, that molecular weight limitation or, excuse me, that mole fraction limitation that we just saw in the patent. It states trihguoracetyl co-polymer-1 having over 75 percent of its molar fraction within the molecular weight range of about two kilodaltons to about 20 kilodaltons, and that's found in claims one to three of the '430 patent, claim one of the '476 patent, and claim one of the '161 patent.
Q. Thank you. Now does the synthetic group used by Sandoz and Momenta, does it make use of trihguoracetyl co-polymer-1?
A. Yes, it does.
Q. And were you able to calculate the molar fraction of Sandoz

and Momenta's trihguoracetyl co-polymer-1 intermediate as used in the manufacture of their product?

A. Yes, I was.

Q. And what data were your calculation based on?

A. It was based upon the data that was supplied to us on the secure flash drive.

Q. Are those the same molecular weight distribution data you were provided for co-polymer-1?

A. Yes, they are.

Q. Was Dr. Winter involved in these calculations, Dr. Grant?

A. Yes, he helped me.

Q. And what was his involvement in this calculation?

A. His involvement was exactly the same involvement that he had in the previous calculation. I told him how to extract the data and to -- what calculations to do on it.

Q. Did he perform any independent calculations on his own data?

A. No, he didn't do anything other than what I instructed him to do.

Q. Now, very briefly, Dr. Grant can you explain how you calculate the TFA co-polymer-1 molar fraction from the co-polymer-1 distribution data?

A. Yes. If you recall that slide that we just had up, that small string of co-polymer-1 with the TFA on the lysine groups, the TFA has a discreet molecular weight. So from the mole

ratio of, or the mole fraction of the co-polymer-1 substance, we can determine how many lysines in there and we can then determine how many TFA lysines would be in there, and that would allow me or allow us to just to have a simple conversion factor to convert the molecular to co-polymer-1 to the molecular weight of TFA co-polymer-1.

Q. And so if I understand correctly, the amount of TFAs related to the amount of lysine in the co-polymer-1?

A. That's correct.

Q. And, how did you determine the amount of lysine in Sandoz Momenta products?

A. The ANDA gave us the numbers for the mole percentage of lysine in their products.

Q. Now, did you create a slide that shows the molecular weight values that you calculated for Sandoz's trihguoracetyl co-polymer-1?

A. Yes, I did.

Q. Let's look at the next slide. Dr. Grant, could you explain what's shown on slide 40, please?

A. Yes, this is a summary of the results of my calculation. On the left-hand side are the different lots that we performed our calculations on, and on the right-hand side under the heading percent TFA molar fraction between two and 20 kilodaltons are the values that I determined the percentage.

Q. Okay. And, Dr. Grant, what's the range of values for the

percent TFA molar fraction between two and 20 kilodaltons?
A. As shown on this slide, the range of values were between greater than or equal to 89.69 percent and greater to or equal to 92.82 percent.
MR. JAMES: And, your Honor, we would offer this slide as evidence under Federal Rule 1006 as a summary of the calculation that he performed on the data.
MR. ACKER: No objection, your Honor.
THE COURT: All right admitted.
(Plaintiff's Exhibit 40 received in evidence)
Q. Dr. Grant, have you made a determination as to which of the trihguoracetyl co-polymer-1 limitations are met by Sandoz's product?
A. Yes, I have.
Q. Let's look at the next slide. Dr. Grant, could you explain what's shown here, please?
A. Well, again, this is just the data that we had on the previous slide. It shows the lot numbers, it shows the results of my calculations, and then on the very far right-hand column, excuse me, it shows the molar fraction claim limitation that applies.
Q. So which of the lots that you analyzed meet the trihguoracetyl co-polymer-1 claim limitation of the asserted claims?
A. In My opinion, all of these lots meet that claim.

Q. Now, Dr. Grant, do you have an opinion as to whether if Sandoz and Momenta used the synthetic process outlined in their ANDA to make glatiramer acetate, whether it would produce an intermediate that satisfies the TFA copolymer-one molar fraction limitations?

A. Yes. If Sandoz meant to use the process outlined in their ANDA, all of their product would meet the claim limitation shown here.

Q. Now, Dr. Grant, let's turn to the analysis of the Mylan and Natco product. Have you reviewed Mylan and Natco's submission to the FDA regarding their product?

A. Yes, I have.

Q. And have you formed an opinion as to whether the generic Copaxone that's proposed by Mylan and Natco meets the average molecular weight limitations of the asserted claims?

A. Yes, I have. It's my opinion that their product meets the average molecular weight certification of the claims.

Q. Dr. Grant, could you turn to plaintiff's trial exhibit 318 in your binder.

A. Okay.

MR. JAMES: Your Honor, I just want to say we're at a sort of a natural stopping point here. We're going to go through the Mylan data. It will go faster than the Sandoz analysis, but it will go on for a little while. Would you like to for me to continue to the end or would you like to pick this

up in the morning?

THE COURT: It looks like everybody's tired.

MR. JAMES: I believe that's my fault.

THE COURT: Well, we'll adjourn then and we can start up with Mylan tomorrow.

MR. JAMES: Thank you, your Honor.

THE COURT: 9:30.

(Adjourned to September 8th, 2011 at 9:30 a.m.)

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PLAINTIFF EXHIBITS

DEFENDANT EXHIBITS